IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Ruggero FARIELLO *et al.*	Docket No:	373987–011 US (102895)
Serial No.:	10/559,982	Confirmation No.:	6583
Filed:	February 2, 2006 (§371)	Group Art Unit:	1617
For:	METHODS FOR THE TREATMENT OF PARKINSON'S DISEASE	Examiner:	Sahar JAVANMARD

THIRD DECLARATION OF C. WARREN OLANOW UNDER 37 C.F.R. § 1.132

I, **C. WARREN OLANOW,** M.D., FRCPC, declare and state as follows:

1. This is the third Declaration that I have submitted in support of U.S. patent application no. 10/559,982.

2. Since my Second Declaration was filed, one reference that I had listed as being "in press" has since been published,

- Olanow *et al.*, "Dopaminergic transplantation for Parkinson's disease: current status and future prospects," *Ann. Neurol.* 66(5):591-6 (2009),

and the following references of which I am an author, which are neither listed in the *Curriculum Vitae* attached to my First Declaration nor mentioned in my Second Declaration, have also now been published:

- Bartus *et al.*, "Bioactivity of AAV2-neurturin gene therapy (CERE-120): Differences between Parkinson's disease and nonhuman primate brains," *Mov. Disord.* (2010) (Nov 18 Epub ahead of print);
- Marks *et al.*, "Gene delivery of AAV2-neurturin for Parkinson's disease: a double-blind, randomised, controlled trial," *Lancet Neurol.* 9(12):1164-72 (2010);
- Olanow *et al.*, "Defining disease-modifying therapies for PD— a road map for moving forward," *Mov. Disord.* 25(12):1774-9 (2010);

- Stocchi *et al.*, "Initiating levodopa/carbidopa therapy with and without entacapone in early Parkinson disease: the STRIDE-PD study," *Ann Neurol.* 68(1):18-27 (2010);
- Olanow *et al.*, "The delayed-start study in Parkinson disease: can't satisfy everyone," *Neurology* 74(14):1149-50 (2010);
- Obeso *et al.*, "A changing journal for a changing field," *Mov. Disord.* 25(3):255-6 (2010);
- Tayarani-Binazir *et al.*, "Pramipexole combined with levodopa improves motor function but reduces dyskinesia in MPTP-treated common marmosets," *Mov. Disord.* 25(3):377-84 (2010), *and*
- Cho *et al.*, "Frequency-velocity mismatch: a fundamental abnormality in parkinsonian gait," *J. Neurophysiol.* 103(3):1478-89 (2010).

The terms of my engagement have not changed, and I specifically reaffirm paragraphs 12 – 15 of my First Declaration. The views I am expressing in this Third Declaration are entirely my own, and have not been influenced by any economic or professional interest in the outcome. The views expressed in this third Declaration do not necessarily reflect the views of Mount Sinai School of Medicine, Mount Sinai Medical Center, or any other organization or entity for which I work, consult, or with which I am affiliated.

3. Before discussing the unexpected properties demonstrated by safinamide in recent clinical trials – properties that have long been sought by clinicians who treat patients with Parkinson's disease (PD) – it is important to review certain basic principles that inform and guide current therapy. These principles are well-known. They are also well-documented, and in the sections below I quote supporting literature for emphasis, where appropriate.

A. **Four decades after its introduction, levodopa remains the most effective treatment for Parkinson's disease and the "gold standard" against which other therapies must be compared. Indeed, no medical or surgical therapy that is currently available has been demonstrated to provide antiparkinsonian benefits that are superior to that which can be achieved with levodopa.**

* * *

"Currently, the best treatment for Parkinson's is levodopa (Sinemet or Madopar) which is converted in the brain into dopamine."[1]

* * *

"L-dopa[2] is the most effective symptomatic therapy for Parkinson disease (PD). No other medical or surgical intervention has been shown to provide greater antiparkinsonian efficacy."[3]

* * *

"Levodopa is the most effective drug for the symptomatic treatment of PD and the gold standard against which new therapies must be measured. Indeed, no other medical or surgical therapy currently available has been shown to provide antiparkinsonian benefits superior to what can be achieved with levodopa. Virtually all patients with PD experience clinically meaningful benefits with levodopa treatment, with improvements in activities of daily living, quality of life, independence, and employability. Benefits are usually seen in all stages of the disease and can be particularly noteworthy in patients with early PD, in whom the drug can control virtually all of the classic motor features."[4]

* * *

1 Macleod *et al.*, "Monoamine oxidase B inhibitors for early Parkinson's disease (review)," *Cochrane Database of Systematic Reviews* 2005, Issue 3, Art. No.: CD004898 ("Macleod") (attached hereto as Exhibit A).

2 The term "L-dopa" is synonymous with "levodopa."

3 Stocchi *et al.*, "Initiating Levodopa/Carbidopa Therapy With and Without Entacapone in Early Parkinson Disease: The STRIDE-PD Study," *Ann. Neurol.* 68:18–27 (2010) ("*STRIDE-PD*") at 18 (attached hereto as Exhibit B).

4 Olanow *et al.*, "The scientific and clinical basis for the treatment of Parkinson disease," *Neurology* 72 (21 Suppl 4):S1-136 (2009) ("*2009 Algorithm*") (of record) at S18, col. 2.

B. **However, chronic levodopa treatment is associated with side effects, known as motor complications: motor fluctuations, such as "wearing off," which constitutes a loss of the motor benefit prior to the ensuing dose, and involuntary movements, known as dyskinesia. These levodopa-induced motor complications may be mild in the early stages of the illness, but can become severe and disabling to PD patients in the more advanced stages. The cause of levodopa-induced motor complications is not precisely known, but is directly related to the levodopa dose – in particular, higher doses of levodopa are associated with an increased risk and increased frequency of dyskinesia.**

* * *

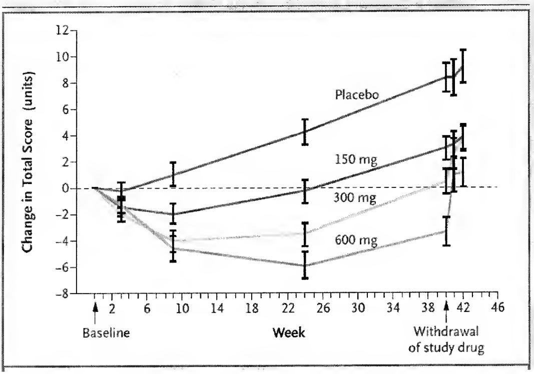
"Chronic levodopa treatment is frequently associated with the development of motor complications. These can be divided into two major subgroups, motor fluctuations and dyskinesia. Motor fluctuations consist of alterations between periods when patients respond to levodopa and experience relatively good mobility and motor function ('on' periods), and periods when the medication does not satisfactorily control motor disability and the response is suboptimal ('off' periods).... Levodopa-induced dyskinesias are involuntary movements that are most often seen in association with the peak plasma levodopa concentration and the maximal clinical response (peak-dose dyskinesias)... . Dyskinesias may be mild and of greater concern to the family than to the patient, or severe and a source of considerable disability to the patient.... **Motor fluctuations can usually be reversed by increasing the dose of levodopa, but this often leads to worsening of dyskinesia. In contrast, dyskinesias tend to disappear with the reduction or elimination of levodopa, but this is usually associated with deterioration in parkinsonism**.... With advancing disease, ... it becomes increasingly difficult to find a dose of levodopa that is both effective and does not cause dyskinesia. In the extreme, patients may cycle between 'on' periods, which are complicated by dyskinesias, and 'off' periods, in which they are akinetic and severely parkinsonian. At this stage, levodopa-induced motor complications can be extremely difficult to control and represent a major source of disability for the patient. **Eventually, it may become impossible to delineate a dose of levodopa that provides motor benefit without inducing dyskinesia**."[5]

* * *

Although these levodopa-related phenomena have long been appreciated, the Earlier *vs* Later Levodopa Therapy in PD (ELLDOPA) study was the first double-blind, placebo-controlled trial to assess the safety and efficacy of different doses of levodopa. The following figure, reproduced from the original report of the ELLDOPA Study results in the New England Journal

[5] *2009 Algorithm,* at S22 – S23 (emphasis added).

of Medicine,[6] dramatically confirms the prior anecdotal understanding that increasing doses of levodopa provide increasing degrees of motor benefit (seen as *decreases* in total score):



* * *

> "This dose–response, placebo-controlled clinical trial evaluating the effect of levodopa in patients with early Parkinson's disease showed a strikingly impressive dose–response clinical benefit: the higher the dose, the stronger and more lasting the benefit…."[7]

* * *

> "A strong dose–response benefit was detected during the period in which the medication was administered…."[8]

* * *

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[6] Fahn *et al.*, "Parkinson Study Group. Does levodopa slow or hasten the rate of progression of Parkinson disease? The results of the ELLDOPA study," *N. Eng. J. Med.* 351:2498-2508 (2004) ("ELLDOPA") (of record), FIG. 2.

[7] ELLDOPA, at 2506.

[8] ELLDOPA, at 2502.

At the same time, however, the enhanced motor benefit obtained with increasing doses of levodopa was demonstrated to be associated with increased frequency of dyskinesia and "wearing off," as shown in this excerpt from the ELLDOPA publication's Table 3 (emphasis added):

Adverse Events.*

Adverse Event	Placebo (N=90)	Levodopa			P Value for Trend
		150 mg/day (N=92)	300 mg/day (N=88)	600 mg/day (N=91)	
		number (percent)			
Dopaminergic effects					
Dyskinesia	3 (3.3)	3 (3.3)	2 (2.3)	15 (16.5)	<0.001
Dystonia	19 (21.1)	19 (20.7)	14 (15.9)	12 (13.2)	0.30
Freezing of gait	13 (14.4)	9 (9.8)	6 (6.8)	5 (5.5)	0.15
On–off	3 (3.3)	1 (1.1)	0	3 (3.3)	0.26
Wearing off	12 (13.3)	15 (16.3)	16 (18.2)	27 (29.7)	0.06

Note that the frequency of dyskinesia increases from 3.3% to 16.5% of study patients as the levodopa dose is increased from 150 mg/day to 600 mg/day; similarly, "wearing off" increases in frequency from 13.3% to 29.7% of patients as the dose is increased.

* * *

> "High doses ... were associated with a greater frequency of adverse events such as dyskinesia."[9]

* * *

> "The ELLDOPA study demonstrated that higher doses of L-dopa are associated with greater symptomatic effects, but increased motor complications."[10]

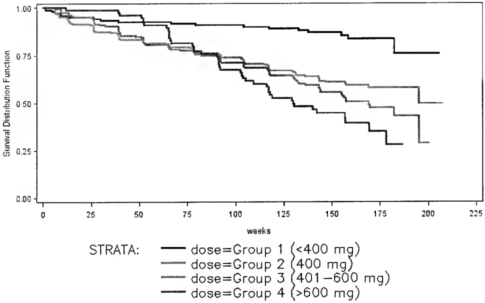
* * *

The dose-related increased risk of dyskinesia with increasing doses of levodopa was more recently confirmed by the long-term, placebo-controlled, double-blind, STRIDE-PD study. The following figure, constructed from STRIDE-PD study data, presents Kaplan-Meier curves demonstrating time to development of dyskinesia (decreases from 1.00) as a function of time and of levodopa dose.[11]

9 *ELLDOPA*, at 2506.

10 *STRIDE-PD*, at 19.

11 Manuscript in preparation.



The figure demonstrates that the higher the levodopa dose, the greater the chances of developing dyskinesia, and the shorter the time to development of dyskinesia. In addition, the frequency of dyskinesia in each group – a static measure – was shown to be directly correlated with levodopa dose, with the highest dose inducing the greatest frequency of dyskinesia in patients. During the course of this study, the frequency of dyskinesia, by treatment group, was:

- Group 1 (< 400 mg levodopa) – 12.1%;
- Group 2 (400 mg levodopa) – 36.8%;
- Group 3 (401 – 600 mg levodopa) – 45.3%; *and*
- Group 4 (> 600 mg levodopa) – 55.8%.

Thus, higher doses of levodopa are associated with enhanced motor benefits, but are also associated with a potentially disabling increased risk and increased frequency of dyskinesia and wearing off.

The precise reason why levodopa causes motor complications such as dyskinesia is not known, but is thought to relate to the non-physiological replacement of dopamine in the brain by oral administration of levodopa.

* * *

"The precise mechanism responsible for why levodopa is so dyskinesiogenic is not known, but increasing information suggests that it may relate to replacement of dopamine in a nonphysiological manner."[12]

* * *

"Dopamine replacement with standard doses of regular levodopa does not make the basal ganglia physiologically normal. Exogenous administration of repeated doses of short-acting levodopa (half-life of about 60–90 min) leads to large and uncontrolled oscillations in striatal and synaptic dopamine concentrations, probably due to the loss of dopamine terminals and their capacity to buffer fluctuations in striatal dopamine concentrations. This leads to a change from the normal situation in which dopamine receptors are continuously exposed to dopamine, to one in which they are exposed to abnormally high or abnormally low concentrations of the neurotransmitter. This pulsatile stimulation destabilises an already unstable basal ganglia."[13]

* * *

[12] Olanow, "Levodopa/Dopamine Replacement Strategies in Parkinson's Disease—Future Directions," *Mov. Disord.* 23(Suppl. 3): S613–S622 (2008) at S614 (attached hereto as Exhibit C).

[13] Olanow *et al.*, "Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications," *Lancet Neurology* 5:677-687 (2006) at 680 (attached hereto as Exhibit D).

C. As a consequence, the treating physician is presented with a dilemma, and frequently cannot provide patients with optimal treatment. In the early stages, the levodopa dosage can be titrated in an attempt to achieve an acceptable compromise between motoric benefit, on the one hand, and dyskinesia, on the other. In later stages, however, patients may experience disability no matter how levodopa is administered. As a compromise, physicians often administer levodopa in dosages that provide suboptimal motor benefit in order to minimize the risk of dyskinesia. Thus PD patients in the modern era are often undertreated in order to prevent the development of potentially disabling dyskinesia.

* * *

"The [STRIDE-PD] study confirms that higher doses of L-dopa are associated with an increased risk of dyskinesia, and supports careful L-dopa dose titration, **using the lowest dose of L-dopa that provides satisfactory clinical control**." [14]

* * *

Because the prevailing practice of downward titration to avoid dyskinesia frequently leads to under-treatment of parkinsonian motor symptoms, we felt compelled to add the following statement immediately following the recommendation to use "the lowest dose of L-dopa that provides satisfactory clinical control": "[h]owever, the authors caution physicians against withholding the optimal L-dopa dose from patients who cannot be satisfactorily controlled with other medications."[15]

D. The inability to administer levodopa at doses that provide optimal motoric benefit presents a longstanding, and unsolved, clinical need.

* * *

"40 years after the introduction of levodopa, there is a paucity of information on how to maximize benefits and minimize side effects with this drug."[16]

* * *

[14] *STRIDE-PD* at 26 (emphasis added).

[15] *STRIDE-PD* at 26.

[16] *2009 Algorithm*, at S20.

> "Thus, the development of a treatment strategy that provides the benefits of L-dopa with reduced motor complications remains among the major unmet medical needs in PD."[17]
>
> * * *
>
> "[T]he ability to deliver levodopa so as to provide symptomatic benefits without complicating dyskinesia or motor fluctuations would represent a major advance in the treatment of PD."[18]
>
> * * *

Surgical therapies such as Deep Brain Stimulation (DBS) are now widely employed as a treatment for advanced Parkinson's Disease.[19] However, DBS involves passing a series of needles through the brain and permanently implanting foreign materials into the body. Accordingly, it is associated with complications related to (*i*) the surgical procedure (hemorrhage, infarction, tissue damage), (*ii*) the mechanical system (lead displacement, infection, wire fracture), and (*iii*) electrode stimulation (depression, suicidal ideations, sensory disturbances, motor twitches).[20] DBS has not been shown to provide anti-parkinsonian benefits that are superior to what can be achieved with levodopa, and surgeries such as DBS are primarily used to treat the motor complications associated with levodopa therapy.

> * * *
>
> "If medical therapies could be developed that provide benefits without inducing motor complications, the need for currently available surgeries would be dramatically reduced."[21]
>
> * * *

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[17] *STRIDE-PD*, at 19.

[18] Lang *et al.*, "Progress In Clinical Neurosciences: A Forum on the Early Management of Parkinson's Disease," *Canadian J. Neurol. Sci.* 32:277-286 (2005) at 277-278 ("Lang") (attached hereto as Exhibit E).

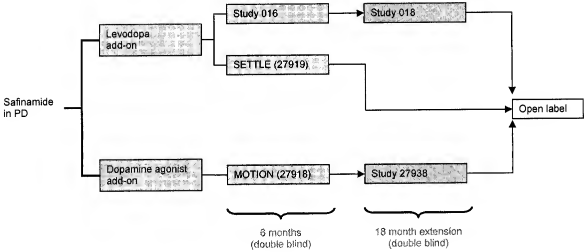
[19] *2009 Algorithm*, at S55-S64.

[20] The Deep Brain Stimulation for PD Study Group (Obeso and Olanow, corresponding authors), "Deep brain stimulation of the subthalamic nucleus or globus pallidus pars interna in Parkinson's disease, *New Eng. J. Med.* 345:956-963 (2001) (of record).

[21] *2009 Algorithm* at S63.

4. Safinamide has the potential to satisfy this unmet need. As detailed below, phase III clinical trials have demonstrated that safinamide ***increases the motoric benefit*** of concomitantly administered stable and optimal doses of levodopa without ***increasing, and potentially decreasing, the risk and severity of dyskinesia***.

5. The following flow chart[22] schematizes the ongoing phase III clinical trial program testing the efficacy of safinamide both as an "add-on" to stable and optimized doses of levodopa (top half of the figure), and separately, as an "add-on" to stable doses of dopamine agonists ("DA") (bottom half of the figure). These clinical trials are being funded by Newron Pharmaceuticals SpA, whom I understand to be the owner of the present patent application, and Merck Serono SA, whom I understand to be the exclusive licensee of the patent application.



I understand that the claims currently under examination are drawn to the addition of safinamide to stable doses of levodopa, and I will therefore confine my comments to the 016 and 018 studies, and will not be discussing the addition of safinamide to stable doses of dopamine

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22 *Adapted from*, Newron Pharmaceuticals SpA, "Safinamide: Study 018 Top-Line Results," Investor and Analyst Call Presentation, November 4, 2010 (available online at http://www.newron.com) ("*Study 018 Presentation*") (attached hereto as Exhibit F).

agonists (which are being evaluated in the MOTION and 27938 studies shown in the flow chart above).[23]

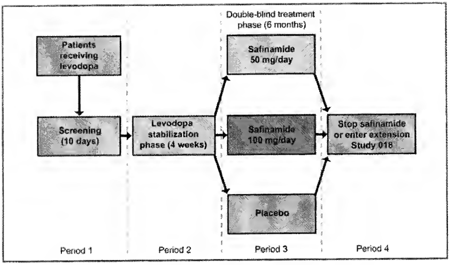
6. The 016 Study was a prospective, randomized, placebo-controlled, double-blind 6 month (24 week) study conducted in multiple centers throughout the world. The results of this study were recently presented at the Movement Disorder Society symposium held in Buenos Aires in June 2010,[24] and the data are currently being prepared for publication. Patients recruited into the study had idiopathic Parkinson's disease of greater than three years' duration, were being treated with stable and optimized doses of levodopa, and were experiencing motor fluctuations with > 1.5 hours of "OFF" time per day. Prior to entry into the study, efforts were made to titrate the dose of levodopa so as to maximize clinical benefit and minimize "OFF" time and dyskinesia. Patients were then randomly assigned to one of three treatment arms: (*i*) addition of placebo, (*ii*) addition of 50 mg/day safinamide, or (*iii*) addition of 100 mg/day safinamide. In each of the groups, the optimized and stable dose of levodopa was maintained for the duration of the study. The design is schematized in Meshram FIG. 1, reproduced below:

[23] It should be noted, however, that dopamine agonists (DA) are primarily used to provide symptomatic anti-parkinsonian benefits in the treatment of early PD, so as to delay the introduction of levodopa and the consequent risk of levodopa-induced dyskinesia and motor fluctuations. Dopamine agonists are not as effective as levodopa, and thus patients eventually require levodopa, and thus eventually become subject to the risk of levodopa-induced motor complications, including dyskinesia. If the efficacy of dopamine agonists could be enhanced, it would further delay the time until levodopa treatment is required. To date, no agent other than levodopa has been demonstrated to enhance the efficacy of a dopamine agonist in a double blind trial.

Preliminary studies with safinamide indicate, however, that when used as an adjunct to a dopamine agonist it enhances the symptomatic benefits of the agonist. Stocchi *et al.*, "Improvement of motor function in early Parkinson disease by safinamide," *Neurology* 63(4):746-8 (2004) (of record).

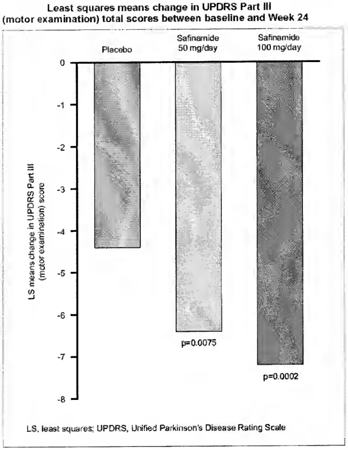
[24] Meshram *et al.*, "Safinamide as add-on to levodopa improves motor function without worsening dyskinesia in patients with mid-late Parkinson's disease," Poster 359, Movement Disorder Society 14th International Congress, Buenos Aires, Argentina, 13-17 June 2010 ("*Meshram*") (of record).

Study design



A total of 669 patients participated in the study and were randomized to one of the treatment arms.

7. The results showed that the addition of both 50 mg/day and 100 mg/day of safinamide to stable and optimized doses of levodopa resulted in a statistically significant and dose-related improvement in motor function, measured as a decrease in Part III of the Unified Parkinson's Disease Rating Scale ("UPDRS Part III"), which is a composite measure of motor function. This is illustrated in Meshram Figure 3, reproduced below:

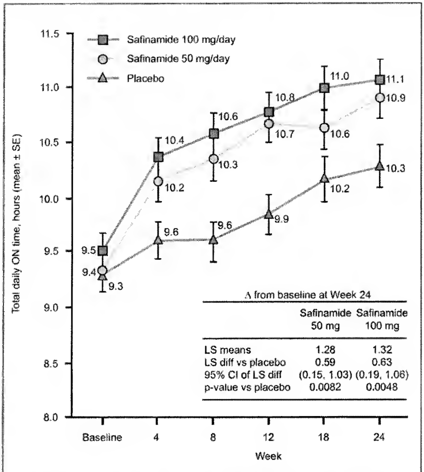


This improvement in motor function was accompanied by a significant increase in "ON" time (periods in which Parkinson motor features are well controlled)[25] at both doses of safinamide. Again this improvement was dose-related, as illustrated in Meshram Figure 2, reproduced below.[26]

[25] And commensurate reduction in "OFF" time (periods in Parkinson motor features are poorly controlled).

[26] Meshram, FIG. 2.

Mean change in ON time (ON without dyskinesia plus ON with minor dyskinesia) during the course of the study



Using an ANCOVA analysis, all time points after baseline were statistically significant when compared with placebo, with the exception of safinamide 50 mg/day at Week 18 (p=0.0739). CI, confidence interval; LS, least squares; SE, standard error

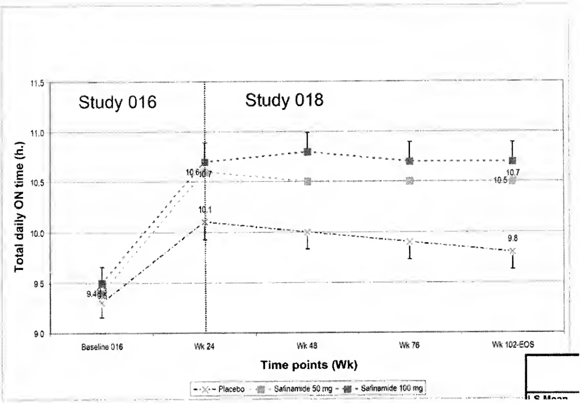
Critically, this improvement in motor function and in "ON" time was achieved **<u>without any increase in dyskinesia</u>**, as assessed by both the Unified Parkinson's Disease Rating Scale ("UPDRS") and the Dyskinesia Rating Scale ("DRS"). These results, as well as those for the separate components that contribute to the composite UPDRS III score, are presented in Meshram Table 3, reproduced below.

Least squares means change in motor and dyskinesia scores between baseline and Week 24			
Parameter	**Placebo (n=222)**	**Safinamide 50 mg/day (n=223)**	**Safinamide 100 mg/day (n=224)**
Motor			
UPDRS III, bradykinesia	-1.6	-2.6 (p=0.014)	-2.7 (p=0.005)
UPDRS III, rigidity	-1.1	-1.5 (p=0.060)	-1.6 (p=0.017)
UPDRS III, postural instability gait disorder	-0.2	-0.2 (p=0.278)	-0.3 (p=0.006)
UPDRS II, freezing when walking	-0.2	-0.2 (p=0.730)	-0.3 (p=0.040)
Dyskinesia			
UPDRS IV, dyskinesia	0.1	-0.1 (p=0.171)	-0.1 (p=0.0828)
UPDRS IV, dyskinesia and dystonia	-0.0	-0.1 (p=0.072)	-0.1 (p=0.094)
DRS	-0.2	-0.2 (p=0.2992)	-0.3 (p=0.2743)

DRS, Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale

8. Study 018 was a double-blind, placebo-controlled extension of the 016 study in which patients who had completed the 6-month (24 week) trial were then continued for an additional 18 months in the same treatment arm to which they had initially been randomized. The improvement in "ON" time observed with both doses of safinamide at 6 months in the 016 study was maintained over the course of the additional 18 months of follow up. Again the benefits achieved with safinamide were dose-related, as shown on the figure below:[27]

[27] *Reproduced from*, Study 018 Presentation.



I am not aware of any medical therapy that has been demonstrated to provide such a sustained motor benefit (increased "ON" time) in a double blind trial of this duration. Furthermore, this sustained improvement in motor function **was not accompanied by any increase in dyskinesia**, as measured using the dyskinesia rating scale ("DRS"). Indeed, there was a trend, observed at both doses of safinamide, **to reduce the dyskinesia severity** in a dose-related fashion, even as the drug simultaneously improved motor function (see figure below):[28]

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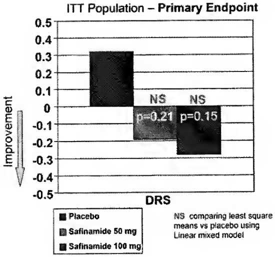
[28] *Figure reproduced from,* Study 018 Presentation. "ITT", intention-to-treat; "NS", not statistically significant.



As discussed above, this contrasts with what is seen with levodopa alone, where increased doses are associated with increased motor benefit, but with ***increased*** dyskinesia.

9. The 016 and 018 Studies demonstrate that safinamide provides sustained anti-parkinsonian motor benefit when added to stable and optimized doses of concurrently administered levodopa, without causing a concomitant increase in, and indeed tending to reduce, dyskinesia. If safinamide is approved by FDA, these properties would help to address a long-sought, unmet, critical need in the management of PD.

10. Two aspects of the 016 and 018 clinical trials warrant further comment.

11. *First*, as discussed above, all patients in the 016 study were being treated with levodopa at the time of enrollment. As would be expected, levodopa dosages differed among patients as each patient's levodopa dosage had been individually titrated by his or her treating physician to achieve an optimal balance between improved motoric function and levodopa-induced side effects, notably dyskinesia.

12. *Second*, most of the patients enrolled in Study 016 (and who thus continued into Study 018) were also being treated with standard anti-parkinsonian agents in addition to levodopa (*e.g.*, dopamine agonists, COMT inhibitors, anticholinergics, and amantadine). The

concurrent use of multiple drugs – colloquially, "*polypharmacy*" – is common in managing patients with Parkinson's disease as treating physicians attempt to provide anti-parkinsonian motor control while minimizing motor complications (motor fluctuations and dyskinesia).[29] Clinical trials of new Parkinson's disease interventions typically include such patients in the trial population – particularly clinical trials that include mid- to late-stage Parkinson's disease patients. In the face of such disparity in underlying patient treatments, the critical statistical requirement is that patients be properly randomized so that the different underlying treatment regimens are equally distributed across the different treatment groups – just as we randomize with respect to differences in age, sex, race, and (for most such trials) disease severity. Randomization permits the effect of the studied intervention to be observed above an inhomogeneous background.[30] This randomization was successfully achieved in the 016/018 studies – the table below[31] shows the distribution of anti-parkinson medications in the three treatment groups upon entry into Study 016:

	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Baseline OFF time (hours) (SD)	5.3 (2.06)	5.2 (2.08)	5.2 (2.16)
Baseline ON time (hours) (SD)	9.30 (2.155)	9.37 (2.259)	9.52 (2.426)
Baseline UPDRS Part III ON (SD)	28.7 (12.03)	27.3 (12.67)	28.3 (13.30)
% of patients with Troublesome Dyskinesia (≥ 30 mins)	32.8 %	32.3 %	29.5 %
PD Treatment			
Levodopa	222 (100.0%)	223 (100.0%)	224 (100.0%)
Dopamine Agonist	136 (61.3%)	142 (63.7%)	128 (57.1%)
Anticholinergic	86 (38.7%)	73 (32.7%)	85 (37.9%)
Entacapone	56 (25.2%)	52 (23.3%)	55 (24.65)
Stalevo	33 (14.9%)	30 (13.5%)	36 (16.1%)
Amantadine	32 (14.4%)	29 (13.0%)	30 (13.4%)

29 See *2009 Algorithm.*

30 In addition, to guard against changes in drugs confounding the results of the clinical trial, patients must be on stable doses of these medications for at least 4 weeks prior to entry into the study, and the drug and the dosage must be maintained at a constant level throughout the course of the study if possible.

31 Reproduced from *Study 018 Presentation.*

This use of polypharmacy is not only standard practice in PD clinical trials, it is preferred to designs that exclude such patients and artificially include only patients on levodopa. Studies that include patients on polypharmacy better approximate the realities that will be encountered in the clinic, and thus provide physicians and regulatory authorities with a better sense of what the study intervention is likely to do when it is introduced into general clinical practice. For this reason, it would have been unusual to have only included patients in the 016/018 Studies who were only receiving levodopa.

13. As an example of standard practice, inclusion criteria in the NIH-sponsored trial of fetal nigral transplantation included

> "at least two cardinal features of parkinsonism (tremor, rigidity, bradykinesia), a good response to L-dopa, stable doses of [various] antiparkinsonian medications, and motor complications that could not be controlled with pharmacological therapy."[32]

Similarly in the recently published STRIDE-PD study,

> "[s]ubjects could be taking stable doses of a dopamine agonist or other antiparkinsonian medications (no change in previous 4 weeks)."[33]

There are countless other examples.

14. Thus, the inclusion criteria used for the 016/018 study were appropriate and in keeping with the standard for clinical trials in patients with Parkinson's disease. Further, as the additional drugs were equally distributed by the randomization process among the different treatment groups, neither the disparate dosages of levodopa used among the patients, nor the differences in use of additional therapeutic agents, affected the conclusions of the 016 and 018 studies: safinamide improves the motor benefit provided by a stable dose of levodopa without concomitantly increasing, and indeed possibly decreasing, dyskinesia. These properties are desired and have long been sought in order to satisfy a current unmet need in the management of

[32] Olanow *et al.*, "A double blind controlled trial of bilateral fetal nigral transplantation in Parkinson's disease," *Ann Neurol.* 54:403-414 (2003) (of record).

[33] STRIDE-PD, at 20.

PD. The development of a drug that can achieve these goals would "represent a major advance in the treatment of PD."[34]

15. Safinamide's ability to improve motoric benefit when added to optimized stable doses of levodopa, without increasing (and perhaps decreasing) dyskinesia, was unexpected, and could not have been predicted from safinamide's known ability to inhibit monoamine oxidase-B (MAO-B).

16. MAO-B inhibitors have long been used in treatment of Parkinson's disease. By blocking catabolism of dopamine in the brain, MAO-B inhibitors raise striatal dopamine concentrations; increased dopamine concentrations at the site of the primary neuronal defect in the striatum improves motor symptoms in Parkinson's disease. Safinamide has long been known to inhibit MAO-B,[35] and was on that basis previously predicted to be therapeutically effective in treating Parkinson's disease.[36]

17. However, the increase in dopamine levels occasioned by MAO-B inhibition is well-known **to increase** the frequency and severity of dyskinesia – this should come as no surprise, since the end-result of inhibiting the MAO-B enzyme, increased dopaminergic tone, is effectively the same as the end-result of increasing the dose of levodopa, which is metabolically converted to dopamine. The clinical approach to reducing dyskinesia induced by adding an MAO-B inhibitor to levodopa is thus to **reduce the concurrent levodopa dose**:

* * *

> "MAO-B inhibitors ... may increase dyskinesia in levodopa-treated patients but this can usually be controlled by **down-titrating the dose of levodopa**."[37]

* * *

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34 Lang, at 277-278.

35 Strolin-Benedetti *et al.*, "The anticonvulsant FCE 26743 is a selective and short-acting MAO-B inhibitor devoid of inducing properties towards cytochrome P450-dependent testosterone hydroxylation in mice and rats," *J. Pharm. Pharmacol.*46:814-819 (1994) (of record).

36 Dostert *et al.*, U.S. Pat. No. 5,502,079 (of record).

37 Olanow *et al.*, "Parkinson's Disease And Other Movement Disorders," Chapter 372, in Harrison's Principles of Internal Medicine, 18th ed. (in press), at manuscript page 16 (emphasis added) (attached hereto as Exhibit G).

"There was a marked **levodopa-sparing effect** with MAO-B inhibitors which was associated with a significant reduction in motor fluctuations ... but not dyskinesia."[38]

* * *

18. Safinamide's ability to increase the motor benefit of concurrently administered levodopa **without increasing (and indeed, possibly *decreasing*) dyskinesia** – and thus, the ability to add safinamide to an optimized levodopa treatment regimen without having to reduce levodopa dosage (*i.e.*, to a stable dose of levodopa) – would not have been predicted from its known ability to inhibit the monoamine oxidase-B (MAO-B) enzyme. Indeed, in reporting the results of an open-label pilot study that preceded the phase III 016 Study, Stocchi and colleagues reported that:

"[b]ecause MAO-B was fully inhibited (95%) at all [safinamide] doses tested, we suggest that the[ ] biochemical and symptomatic dose-dependent effects must be related to additional mechanisms of action...."[39]

19. Although the unexpected properties discussed above would alone be sufficient to qualify safinamide as a significant addition to our armamentarium of Parkinson disease treatments, Study 016 provides *suggestions* of additional, and equally unexpected, therapeutic benefits of the drug. Despite the fact that Parkinson's disease has long been considered primarily a motor disorder, mental symptoms such as delirium, anxiety, depression, cognitive impairment, and dementia occur at one time or another in most patients, and can potentially be more disabling than levodopa-responsive motoric dysfunction in levodopa-treated patients.[40] Remarkably, data from the 016 Study suggest that addition of safinamide to clinically optimized, stable doses of levodopa also improves symptoms of depression, a non-motor symptom seen often in mid- to late-stage Parkinson's disease, with improvements reaching statistical significance at 100 mg/day

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38 Macleod, at pages 1 – 2 (emphasis added).

39 Stocchi *et al.*, "Symptom relief in Parkinson disease by safinamide: biochemical and clinical evidence of efficacy beyond MAO-B inhibition," *Neurology* 67 (suppl 2):S24-S29 (2006) (of record), Abstract.

40 Hely *et al.*, "The Sydney Multicenter Study of Parkinson's disease: The Inevitability of Dementia at 20 years," *Mov. Disord.* 6:837-844 (2008) (attached hereto as Exhibit H).

safinamide.[41] The analogous data have not yet been reported from the 18 month Study 018 extension. Earlier studies of safinamide suggest improvement in cognitive function as well, which is unexpected and which will be evaluated in future trials.

20. Based on all of the above, it is my opinion that safinamide is a unique molecule that offers the potential for unique treatment effects in PD. It has been demonstrated to provide anti-parkinsonian benefits to patients receiving optimized and stable doses of levodopa, and does so without increasing dyskinesia, even showing a trend towards reduction of dyskinesia. There is also a suggestion that safinamide might provide benefits with respect to mood and cognition. This combination of benefits is has not been demonstrated with any other antiparkinsonian therapy, was unexpected, and would satisfy a well-documented, longstanding, unmet medical need.

21. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information or belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements and the like so made may jeopardize the validity or enforceability of U.S. Patent Application Serial No. 10/559,982, or any patent that issues therefrom.

Feb 4/2011

Date

C. Warren Olanow, M.D.

[41] Borgohain *et al.*, "Effect of safinamide on depressive symptoms in patients with mid-late stage Parkinson's disease," Poster 324, Movement Disorder Society 14th International Congress, Buenos Aires, Argentina, 13-17 June 2010 (of record).

Exhibits

Exhibit A: Macleod *et al.*, "Monoamine oxidase B inhibitors for early Parkinson's disease (review)," *Cochrane Database of Systematic Reviews* 2005, Issue 3, Art. No.: CD004898.

Exhibit B: Stocchi *et al.*, "Initiating Levodopa/Carbidopa Therapy With and Without Entacapone in Early Parkinson Disease: The STRIDE-PD Study," *Ann. Neurol.* 68:18–27 (2010).

Exhibit C: Olanow, "Levodopa/Dopamine Replacement Strategies in Parkinson's Disease — Future Directions," *Mov. Disord.* 23(Suppl. 3): S613–S622 (2008).

Exhibit D: Olanow *et al.*, "Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications," *Lancet Neurology* 5:677-687 (2006).

Exhibit E: Lang *et al.*, "Progress In Clinical Neurosciences: A Forum on the Early Management of Parkinson's Disease," *Canadian J. Neurol. Sci.* 32:277-286 (2005).

Exhibit F: Newron Pharmaceuticals SpA, "Safinamide: Study 018 Top-Line Results," Investor and Analyst Call Presentation, November 4, 2010 (available online at http://www.newron.com) ("*Study 018 Presentation*").

Exhibit G Olanow *et al.*, "Parkinson's Disease And Other Movement Disorders," Chapter 372, in <u>Harrison's Principles of Internal Medicine</u>, 18^{th} ed. (in press) (manuscript).

Exhibit H Hely *et al.*, "The Sydney Multicenter Study of Parkinson's disease: The Inevitability of Dementia at 20 years," *Mov. Disord.* 6:837-844 (2008).

EXHIBIT A

Monoamine oxidase B inhibitors for early Parkinson's disease (Review)

Macleod A, Counsell C, Ives N, Stowe R

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[Intervention Review]

Monoamine oxidase B inhibitors for early Parkinson's disease

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ABSTRACT

Background

It has been postulated that monoamine oxidase B (MAO-B) inhibitors alrer disease progression in Parkinson's disease (PD). Clinical trials have produced conflicting results.

Objectives

To assess the evidence from randomized controlled trials for the effectiveness and safety of long-term use of MAO-B inhibitors in early PD.

Search strategy

We searched the following electronic databases: Cochrane Central Register of Controlled trials (CENTRAL) (The Cochrane Library Issue 2, 2004), MEDLINE (last searched 18th August 2004) and EMBASE (last searched 18th August 2004). We also handsearched neurology and movement disorders conference proceedings, checked reference lists of relevant srudies and contacted other researchers.

Selection criteria

We sought to include all unconfounded randomized controlled trials that compared a MAO-B inhibitor with control, in the presence or absence of levodopa or dopamine agonists, in patients with early PD and where treatment and follow up lasted at least one year.

Data collection and analysis

Two reviewers independently selected trials for inclusion, assessed the methodological quality, and extracted the data. A small amount of additional data was provided by the original authors. Random-effects models were used to analyse results, where appropriate.

Main results

Ten trials were included (a total of 2422 patients), nine using selegiline, one using lazabemide. The methodological quality was reasonable although concealmenr of allocation was definitely adequate in only four trials. The mean follow up was for 5.8 years. MAO-B inhibitors were not associated with a significant increase in deaths (odds ratio (OR) 1.15; 95% confidence interval (CI) 0.92 to 1.44). They provided small benefits over control in impairment (weighted mean difference (WMD) for change in motor UPDRS score was 3.81 points less with MAO-B inhibitors; 95% CI 2.27 to 5.36) and disability (WMD for change in UPDRS ADL score was 1.50 less; 95% CI 0.48 to 2.53) at one year which, although statistically significant, were not clinically significant. There was a marked levodopa-sparing effect with MAO-B inhibitors which was associated with a significant reduction in moror fluctuations (OR 0.75; 95% CI

0.59 to 0.94) but not dyskinesia (OR 0.97; 95% CI 0.76 to 1.25). The reduction in motor fluctuations was, however, not robust in sensitivity analyses. Although adverse events were generally mild and infrequent, withdrawals due to side-effects were higher (OR 2.36; 95% CI 1.32 to 4.20) with MAO-B inhibitors.

Authors' conclusions

MAO-B inhibitors do not appear to delay disease ptogression but may have a beneficial effect on motor fluctuations. There was no statistically significant effect on deaths although the confidence interval does not exclude a small increase with MAO-B inhibitors. At present we do not feel these drugs can be recommended for routine use in the treatment of early Parkinson's disease but further randomized controlled ttials should be carried out to clarify, in particular, their effect on deaths and motor complications.

PLAIN LANGUAGE SUMMARY

Monoamine oxidase B inhibitors for early Parkinson's disease

Parkinson's disease is a disabling condition of the brain charactetized by slowness of movement, shaking (tremor), stiffness, and in the later stages, loss of balance. Many of these symptoms are due to the loss of certain groups of nerves in the btain, which results in the lack of a chemical called dopamine. Currently, the best treatment for Parkinson's is levodopa (Sinemet or Madopat) which is convetted in the btain into dopamine. Although a very good treatment, levodopa does not slow the progression of the underlying condition and after a while dtug use can cause involuntary movements (dyskinesia), painful leg cramps (dystonia) and a shottened response to each dose (motor fluctuations). Monoamine oxidase B (MAO-B) inhibitors such as selegiline (Eldepryl or Selgene) boost the levels of dopamine by a different mechanism which may teduce the risk of these complications and slow disease ptogression. We reviewed ten controlled ttials (in a total of 2422 patients) that compared giving MAO-B inhibitors with not giving them in people with early Parkinson's to see if it was safe and effective. The results show that, although MAO-B inhibitors do improve symptoms of Parkinson's and delay the need fot levodopa by a few months, they are too weak to have a major effect and do not seem to delay the progression of the condition. They may, however, reduce motor fluctuations although more infotmation is needed to be cettain of this. Although they can cause some side-effects, these are generally mild.

BACKGROUND

Parkinson's disease is a progressive neurodegenerative disorder characterized by a combination of bradykinesia (slowness), tremor (shakiness), rigidity (stiffness) and postural instability (unsteadiness). In most cases the cause remains unknown but there are characteristic changes in the brain including loss of dopaminergic neurons in regions of the brainstem and neuronal inclusions called Lewy bodies. The incidence (Twelves 2003) and prevalence (Tanner 1992) of Parkinson's disease increases dramatically with age and so its impact is set to increase as the population ages.

Since its introduction in 1967, the mainstay of treatment for Parkinson's disease has been levodopa, a dopamine precursor, which replenishes the depleted dopamine and alleviates many of the symptoms and signs (Watts 1997). However, after several years of treatment with levodopa many patients develop unpleasant and potentially disabling motor fluctuations ("wearing-off" and "on-off" phenomena) and dyskinesias (abnormal involuntary movements). These adverse effects occur in approximately 50% of patients after five years of levodopa treatment, and are more common in patients with early-onset Parkinson's disease (Lang 1998). This, and the fact that levodopa probably does not alter the underlying disease progression have led researchers to look for alternative treatments that actually delay the pathogenesis of the disease and cause fewer long-term side-effects.

Monoamine oxidase B (MAO-B) inhibitors block one of the enzymes that breaks down dopamine in the brain and so enhance its effects. Interest in their use in early Parkinson's disease arose from a retrospective observational study which showed improved survival of patients with Parkinson's disease when treated with the MAO-B inhibitor selegiline (Birkmayer 1985). Around the same time, a group of Californian heroin addicts developed severe parkin-

sonism, due to a heroin contaminant, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), that was metabolised by MAO-B to a substance that was neurotoxic to dopaminergic neurons (Langston 1983). MAO-B inhibitors were shown to protect against MPTP toxicity in animal models of Parkinson's disease (Heikkila 1984). It has, therefore, been proposed that a similar mechanism of neurotoxicity may exist in Parkinson's disease due to an, as yet, unidentified environmental toxin against which MAO-B inhibitors may be effective. Furthermore, MAO-B inhibitors may be neuroprotective in Parkinson's disease by reducing the oxidative stress that exists in dopaminergic neurons (Olanow 1996) and some may have anti-apoptotic effects that are independent of inhibition of MAO-B (Maruyama 2002).

The potential benefit of the early use of MAO-B inhibitors was supported by initial clinical trials that showed a delay in the need for levodopa in patients started on selegiline (PSG 1989). This was initially interpreted as a delay in disease progression but was later thought to be simply due to a symptomatic response from the weak dopaminergic activity of selegiline (Calne 1995). The pendulum swung against the early use of MAO-B inhibitors following the publication of another trial that showed worse survival (Lees 1995), although this may have been a chance finding (Breteler 1998). Clearly, with such conflicting evidence, a systematic review of all relevant trials is required to establish the efficacy and safety of MAO-B inhibitors in early Parkinson's disease. The most recently published review (Olanow 1998a) was restricted to selegiline (even though there are two additional MAO-B inhibitors, rasagiline and lazabemide), had poorly described methods, only considered one outcome (death), and did not include the two largest studies.

OBJECTIVES

The objective of this review was to review the evidence from randomized controlled trials for the efficacy and safety of long-term use of MAO-B inhibitors in patients with early Parkinson's disease.

METHODS

Criteria for considering studies for this review

Types of studies

We sought to identify all truly randomized, properly concealed, controlled trials comparing MAO-B inhibitors with control interventions in early Parkinson's disease. We also included studies in which the method of randomization or concealment was unknown. Cross-over studies were excluded as they are not designed to assess long-term effects.

Types of participants

We included trials that recruited patients with early Parkinson's disease, that is trials in which patients were starting parkinsonian treatment for the first time or had started treatment within the last 12 months and where the majority of patients were classified as Hoehn-Yahr stage II or less (i.e. no impairment of balance). Trials including a significant proportion of patients with motor fluctuations (greater than 10%) were excluded. No strict diagnostic criteria for Parkinson's disease were set but the definition used in each trial was recorded.

Types of interventions

We included long-term unconfounded trials comparing any dose of MAO-B inhibitor (currently selegiline, rasagiline or lazabemide) with no treatment or placebo. Thus, trials comparing MAO-B inhibitor and levodopa versus levodopa, or MAO-B inhibitor and a dopamine agonist versus a dopamine agonist, were included. Trials in which additional levodopa or dopamine agonist could be introduced into both arms according to clinical need as the disease progressed were also included. Trials of MAO-B inhibitors in a head-to-head comparison with another drug (for example, MAO-B inhibitor alone versus levodopa alone) were excluded. Trials with treatment or follow up of less than one year's duration were also excluded because we were interested in the long-term effects of treatment rather than short-term symptomatic effects.

Types of outcome measures

(1) To evaluate the effectiveness of MAO-B inhibitors we collected data at the final available follow up on the following outcome measures in each treatment group.
(a) Number of patients who were either dead or disabled (that is, needed help with activities of daily living) from any cause (for example, disease progression, motor fluctuations or dyskinesias). Patients who became disabled and subsequently died were counted only once in this analysis.
(b) Number of deaths.
(c) Disease progression in terms of:
(i) severity of Parkinsonian impairment, disability and quality of life provided that data were reported for the same duration of follow up and the same clinical condition (that is, on or off medication) in the treatment and control groups;
(ii) levodopa requirements including mean levodopa dose and numbers of patients requiring levodopa;
(iii) time to introduction of levodopa or dopamine agonist.
(d) Number of patients with motor fluctuations including wearing off, on/off fluctuations and early morning dystonia.
(e) Number of patients with dyskinesias.
(2) To assess the safety of MAO-B inhibitors, we collected data at final follow up on the following outcome measures in each treatment group.

(a) Number of patients with adverse events such as nausea, postural hypotension and neuropsychiatric effects.
(b) Number of withdrawals due to adverse events.
(c) Total number of withdrawals.
If sufficient trials recorded outcomes at the same point in time (for example, at one year) we sought to analyse outcomes at that time point. The primary outcome measure was the number of people who wete dead ot disabled since this assessed the overall effect of tteatment on a clinically important outcome. It would captute any delay in disease progression or prevention of severe motot complications with treatment but also take into account any inctease in death tate.

Search methods for identification of studies

The following sources and searches were used to identify relevant tandomized controlled trials:
(1) The Cochtane Central Register of Controlled Trials (CENTRAL), (*The Cochrane Library* Issue 2, 2004)
(2) MEDLINE through OVID Gateway (last searched 18th August 2004)
(3) EMBASE thtough OVID Gateway (last searched 18th August 2004)
(4) Online searching of conference proceedings through the ISI Proceedings database (seatched 4th September 2003)
#1 TS=(selegiline OR deprenyl OR deprenil OR eldepryl OR lazabemide OR tasagiline)
#2 TS=(TRIAL OR RANDOM* OR PLACEBO* OR CONTROL*)
#3 #1 AND #2
(5) Handseatching of the following conference proceedings:
Fitst to Seventh International Congress of Movement Disorders (1990 to 2002);
XII International Symposium on Parkinson's Disease (1997);
XIII and XIV International Congress on Parkinson's Disease (1999 and 2001);
XVIth and XVIIth meeting of the World Congress of Neurology (1997 and 2001);
Thirty-seventh to 54th annual meetings of the American Academy of Neurology (1985 to 2002);
One hundred and Tenth to 127th meetings of the American Neurological Society (1985 to 2002);
Sixth and Seventh Meetings of the European Federation of Neurological Sciences (2002 and 2003);
Tenth to 13th meetings of the European Neurological Society (2001 to 2003);
Twenty-ninth to 33rd meetings of the Scandinavian Congress of Neurology (1990 to 2002).
(6) Checking reference lists: we sought to identify any additional references to trials in the published reports of relevant trials.
(7) Previous reviews were checked to identify any missing trials.
(8) Personal communication — we contacted other researchers in the field.

Data collection and analysis

Two reviewers (ADM, RS) independently assessed the titles and abstracts identified from the electronic and other searches and the full text of potentially relevant articles was obtained. The final eligibility of each article, on the basis of the inclusion and exclusion criteria, was checked with a third reviewet (CC). Thete were no disagreements over which studies should be included. Articles teporting the same study were grouped together and the most up-to-date tesults for each outcome wete used for this review.
The methodological quality of each trial was assessed accotding to method of randomization, the blinding of treatment and outcome assessment, the use of placebo control, the completeness of follow-up and whether intention-to-treat analysis was carried out or possible from the published data. We also assessed whether the treatment groups were comparable with regard to demographics, clinical characteristics, the numbet of patients excluded or lost to follow up within each trial and whether the definitions of outcomes and inclusion and exclusion criteria were comparable across the diffetent trials. Data on the number of patients with each outcome event were sought by allocated treatment gtoup, ittespective of compliance and whether or not the patient was subsequently deemed ineligible or otherwise excluded from follow up, to allow an intention-to-treat analysis. All data were exttacted by two reviewers and cross checked. We attempted to contact the authors of the studies for further details if details of randomization ot concealment were unclear or if any data on the outcomes wete missing.
Formal meta-analysis was performed using RevMan 4.2 and whete we could not combine outcome data from different studies (fot example, because the outcomes recorded were too variable) we gave a descriptive summary of the results. For the main analyses the denominator was the number of patients in whom the outcome was assessed. For each outcome we calculated mean duration of follow up weighted for trial size by multiplying the mean duration of follow up for each study by the total trial size then dividing by the total number of participants included for that outcome. We calculated odds ratios (and 95% confidence intervals) for the binary outcomes and, if the results were statistically significant and the duration of follow up was similar between trials, we calculated the absolute risk reductions or increases for a variety of baseline absolute risks. Some trials had significantly different periods of follow up in the two treatment arms and, therefore, we adjusted the results of binary outcomes to take account of this by increasing the number of events in the arm with the shorter follow up by a proportional amount. However, we have also reported the unadjusted results. For continuous outcome measures (for example, impairment), we calculated a mean weighted difference where possible (or a standardized mean difference where different scales

for the same outcome were used). To assess the change in impairment and disability data from baseline to one year, or to the end of the washout period, we had to impute the standard deviations from three studies which only reported the standard deviations for the baseline and final scores. To do this we used the following formula to estimate the variance of the change in score:
$var_{diff} = var_{pre} + var_{post} - 2r\sqrt{(var_{pre}var_{post})}$

where var_{diff} is the variance of the change in score; var_{pre} is the variance of the baseline score; var_{post} is the variance of the final score and r is the correlation between the pre- and post-treatment scores. We assumed a correlation co-efficient of 0.5, which is a conservative estimate, to reduce the chance of false positive results. Continuous data that were obviously skewed were excluded from meta-analysis because the statistical techniques used assume a normal distribution.

For each outcome, the primary analysis was reported from a random-effects model. A fixed-effect model was also used but this did not significantly alter any of the results. Heterogeneity was assessed with both the I^2 statistic (Higgins 2003) (0% indicates no heterogeneity and a value greater than 50% indicates substantial heterogeneity), and the chi squared test. The latter was regarded as significant if the probability value was less than 0.1 because of the low power of the test. There were no discrepancies between these two measures of heterogeneity for any outcomes and so we have only reported the I^2 value in the text. If significant heterogeneity was found, we attempted to identify possible causes for this by carrying out planned subgroup analyses based on:
(1) trial quality - high quality trials (truly randomized, well concealed randomization and double-blind) versus those of lower quality;
(2) the use of levodopa or a dopamine agonist at the beginning of trial - trials with patients on levodopa or a dopamine agonist at the start of a trial versus those studies where patients were started only on an MAO-B inhibitor or control;
(3) the different MAO-B inhibitors;
(4) the duration of follow up - trials with a follow up period greater than five years versus those with follow up less than five years;
(5) the type of early patients recruited - trials using a more strict definition of early disease (that is all patients Hoehn and Yahr II or less and previous treatment less than six months) versus those using less strict criteria.
We assessed the difference between subgroups by calculating a two-tailed z-score using the following formulae for binary and continuous data respectively (Fleiss 1993):
$z = (\ln OR_1 - \ln OR_2) / \sqrt{(var[\ln OR_1] + var[\ln OR_2])}$; $z = (SMD_1 - SMD_2) / \sqrt{(var[SMD_1] + var[SMD_2])}$
where $OR_{1/2}$ and $SMD_{1/2}$ are the combined odds ratios or standardised mean differences from each subgroup and var is the variance of each which was calculated from the 95% confidence intervals by the formula $var[\ln OR] = \{(\ln[upper 95\%CI] - \ln[lower95\%CI])/(2*1.96)\}^2$.
The effect of publication bias was analysed with a funnel plot (Egger 1997) and by calculating the size of an imaginary null trial (OR = 1) that would be required to turn any statistically significant result into a non-significant result, assuming an event rate equal to the average event rate in the control groups. Finally, for statistically significant results from dichotomous data we assessed the effect of missing outcomes from patients excluded or lost after randomization by performing a modified worst-case or best-case sensitivity analysis. For a true worst-case analyses (that is most weighted against treatment) it is usually assumed that all excluded patients in the treatment group had an adverse outcome and all those in the control group had a positive outcome, and vice-versa for a best-case analysis. However, it is often unrealistic to expect this to be the case; so, for a more realistic assessment we performed a modified worst-case or best-case analysis. For the former we assumed the lost patients in the treatment group had the highest rate of poor outcome found in any trial whilst those in the control group had the lowest rate in any individual trial, and vice versa for the modified best-case analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Ten randomized trials, with a total of 2422 patients, met the inclusion criteria and were included in the review. Summary details of these trials are given in the Characteristics of included studies table. Nine studies were excluded (see Characteristics of excluded studies table). Seven of these were too short (treatment and follow up of less than one year) and three studies were confounded, for example comparing MAO-B inhibitor alone versus levodopa or bromocriptine alone. One study, a three-arm randomized trial comparing bromocriptine, selegiline or both in about 150 patients, was published only in abstract form and is awaiting assessment pending further information from the authors (PARJUPAR 1996). No relevant ongoing trials have been identified to date.
All of the included trials recruited only patients with a clinical diagnosis of idiopathic Parkinson's disease, although the precise diagnostic criteria were not usually given. Eight studies excluded patients with dementia; and all except one (UK-PDRG 2001) excluded severe or unstable concomitant diseases. Three studies (California 1989; DATATOP 1993; Norway-Denmark 1999) excluded both very young and elderly patients, two excluded only elderly patients (SELEDO 1999; Swedish PSG 1998), and one (UK 1996) included only patients aged 65 or over. Mean age, adjusted for study size, was 62.8 years. All studies except one (

Finland 1997) enrolled more males than females, five studies with a 2:1 ratio or greater. The mean stage of disease, on the Hoehn and Yahr scale was about two.

Some participants had previously been treated with levodopa although not for more than one year. In four studies the percentage of patients that had previously been treated varied between 15% and 34% (California 1989; Norway-Denmark 1999; PSG 1996; SELEDO 1999). Three other studies (DATATOP 1993; UK-PDRG 2001; US 1995) included only patients who were not on treatment for Parkinson's disease at the time of randomization of whom a small unspecified proportion of participants had previously been treated with levodopa. Three studies (Finland 1997; Swedish PSG 1998; UK 1996) included only patients who had never been treated with levodopa or any other dopaminergic medication. Only two studies met the criteria for a strict definition of early disease (that is restricted to patients in Hoehn and Yahr grades I or II with prior treatment of less than six months (DATATOP 1993; PSG 1996).

In nine studies the MAO-B inhibitor used was selegiline and in one study lazabemide was used (PSG 1996). No studies of rasagiline met the inclusion criteria. All the selegiline studies used either 10 mg daily or 5 mg twice daily. The PSG study used lazabemide at four different doses twice daily (12.5 mg, 25 mg, 50 mg, 100 mg) and for the purposes of this review the results from these dosage groups were combined because no dose-response relationship was found.

In six trials the treated patients received selegiline (California 1989; DATATOP 1993; Finland 1997; Swedish PSG 1998; UK 1996) or lazabemide (PSG 1996) alone from the outset. In the Californian and UK trials patients received selegiline or placebo until levodopa was clinically indicated, at which point the participants were withdrawn from further evaluation. The Finnish and Swedish studies consisted of two phases: the first, until the patients required levodopa, was treatment with just selegiline or placebo; the second phase involved the addition of levodopa to both groups. The Swedish study has only reported phase one at present. The DATATOP study was a 2 by 2 factorial design with selegiline and tocopherol (vitamin E). In this review we have recorded outcomes for selegiline and placebo regardless of the use of tocopherol which was found to be ineffective. Levodopa was added to the treatment regimen, as required, following washout. After an interim analysis at two years, the protocol was modified and all participants received selegiline. Subsequently the design was modified again and the participants were re-randomized to remain on selegiline or to have it withdrawn. Because of these changes, and the multiple publications, analysis of DATATOP by initial randomization was problematic although we have tried to record outcomes by the original randomization.

Three trials used levodopa and selegiline treatment from the outset of the trials (Norway-Denmark 1999; UK-PDRG 2001; SELEDO 1999). Patients in the Norwegian-Danish trial and the SELEDO study received either selegiline or placebo in addition to levodopa until the endpoint or up to five years. In the Norwegian-Danish study the endpoint was the need for additional medication whilst in SELEDO it was a 50% increase in the levodopa dose. The UK-PDRG study was an open trial with three arms: levodopa alone, selegiline and levodopa, and bromocriptine alone. In this review we have excluded the bromocriptine patients except for a small number who were quickly re-randomized into the first two arms because they were unable to tolerate bromocriptine (UK-PDRG (RR) 1998). The numbers of deaths in these patients were reported separately and have been included as a separate trial. Ten years after the UK-PDRG trial began (mean follow up of 6.8 years) the selegiline arm was discontinued due to concerns about increased mortality. Follow up continued for another mean 2.4 years.

The final study (US 1995) used a 2 by 2 factorial design to compare selegiline with placebo in the presence of either levodopa or bromocriptine. For the main analyses we have considered the results from the levodopa arms and the bromocriptine arms separately.

Six studies included a washout period after the endpoint to try to assess the effect of MAO-B inhibitors on actual disease progression by attempting to eliminate the confounding of any symptomatic effect. The washout period varied from two weeks (PSG 1996) to two months (Swedish PSG 1998; US 1995).

Three studies had follow up lasting about one year (PSG 1996; UK 1996; US 1995). The Swedish study (Swedish PSG 1998) has published data for patients followed until levodopa was required (selegiline arm: median 12.7 months; placebo arm: median 10.4 months) but follow up is ongoing. One study (California 1989) had a maximum follow up of about three years (mean follow up 1.5 years in the selegiline arm, 0.9 years in the placebo arm) whilst two studies had a maximum follow up duration of five years: Norway-Denmark 1999 (mean follow up 2.9 years in selegiline arm, 3.1 years in placebo arm) and SELEDO 1999 (mean follow up 3.9 years in selegiline arm, 3.6 years in placebo arm). One study had a mean follow up of about six years (Finland 1997) whilst the DATATOP and UK-PDRG studies both had longer duration of follow up for mortality : mean 8.2 years (DATATOP 1993) and 9.2 years (UK-PDRG 2001).

Risk of bias in included studies

Randomization

Methods of randomization were poorly described in most of the studies. Four studies did not give any details of generation of randomization sequence or of concealment of allocation (PSG 1996; SELEDO 1999; Swedish PSG 1998; UK 1996). Further information was not obtained despite writing to the authors. The Californian study (California 1989) used a "biased coin" and another study used a computer to generate the randomization sequence (US 1995), but each gave no details about concealment. Four studies gave sufficient information for us to classify the concealment

as adequate (DATATOP 1993; Finland 1997; Norway-Denmark 1999; UK-PDRG 2001).

Baseline differences between treatment groups

All the studies had similar severity scores in the intervention and control groups at baseline.

Blinding

Blinding of patients, doctors and outcome assessors took place in nine of the trials. The only unblinded trial was the UK study (UK-PDRG 2001). This leaves open the possibility of intervention bias (systematic differences in the care between groups) or measurement bias (systematic differences in the measurement of outcomes). Although the latter should have had no effect on the number of deaths, we cannot discount the possibility that bias was introduced in subjective measures such as disease impairment or disability scales, or in decisions to introduce levodopa.

Exclusions and losses to follow up

Many ttials did not cleatly teport withdrawals so it was impossible to calculate the total numbers of exclusions following randomization and losses to follow up. In addition, losses to follow up varied depending on the time point at which the outcome was measured. As a maximum estimate of the participants not included in the analyses, the total number of withdrawals in all studies was 314 out of 2314 (14%), 169 of 1265 (13.4%) in the intervention group and 145 of 1049 (13.8%) in the control group. However, losses to mortality follow up were fewer because some of the withdrawn participants were included in the analysis of deaths although the ptecise numbers were not always reported.

Intention-to-treat analysis

Most studies did not include withdrawn patients in the analyses. Only one ttial (UK-PDRG 2001) reported tesults based on a true intention-to-treat analysis; DATATOP 1993 reported mortality data only and PSG 1996 teported results on numbers requiring levodopa on an intention-to-treat basis.

Effects of interventions

The 10 included trials varied substantially in reporting particular outcomes so we have more complete data for some outcome measures than for others. All dichotomous outcomes are adverse events so an odds ratio less than one favours treatment with MAO-B inhibitors. For the continuous outcomes a weighted mean difference less than zero favours MAO-B inhibitors.

Dead or disabled at end of follow-up

No trial reported data on the primary outcome.

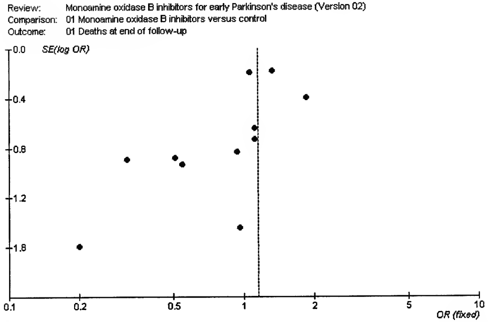
Deaths at end of follow up (comparison 1.1)

All the studies teported data on deaths at the end of follow up. Data were available fot 2389 patients (98.7% of all those randomized). Dutation of follow up vatied considerably between the trials ftom one year to 9.2 years with a mean weighted follow up of 5.8 years. Three studies had data available after the end of official follow up: one study (Finland 1997) reported deaths aftet the trial ended in the final study publication (Myllylä 1997); and furthet data wete available from two studies (Swedish PSG 1998; US 1995) in an individual patient data meta-analysis (Olanow 1998a). Only one study had a significant difference in the duration of follow up in the two treatment arms which was adjusted for in the main analysis (UK-PDRG (RR) 1998).

Overall there was a non-significant increase in deaths amongst patients treated with MAO-B inhibitors compared with those given control (odds ratio (OR) 1.15; 95% confidence interval (CI) 0.92 to 1.44, P value 0.21) with no significant heterogeneity (I^2 value 0%). The odds ratio remained non-significant when the unadjusted data from the UK-PDRG (RR) 1998 study were used (OR 1.10; 95% CI 0.88 to 1.38).

A funnel plot (Figure 1) suggested a publication bias: there wete no small studies showing increased deaths with MAO-B inhibitots. However, repeating the analysis and including only those trials with more than 150 patients (that is removing the potentially biased smaller trials) did not alter the tesults (OR 1.16; 95% CI 0.91 to 1.48). An unpublished study of 560 participants with an odds ratio of 1.32 (the highest unadjusted odds ratio amongst the included studies) would be required to make the overall odds ratio significantly in favour of the control group.

Figure 1. Funnel plot for death at end of follow up



The following pre-specified subgroup analyses showed no significant differences:

(1) High quality (well concealed randomization, double-blind trials) versus lower quality trials: OR 1.06 versus OR 1.22 respectively, P value 0.55.

(2) Trials which used levodopa or a dopamine agonist from the beginning of the trial versus those that used MAO-B inhibitors alone: OR 1.28 versus 1.01, P value 0.30.

(3) Trials of selegiline versus lazabemide: OR 1.17 versus 0.51, P value 0.35.

(4) Trials with follow up greater than five years versus those with shorter follow up: OR 1.24 versus 0.64, P value 0.08).

(5) Trials with a strict definition of early disease versus those with a less strict definition: OR 1.03 versus 1.23, P value 0.45.

Severity of parkinsonism

All the studies reported data on disease progression in some form but this lacked consistency. For example, a variety of different scales were used. Parkinsonian impairment was most commonly reported using the Unified Parkinson's Disease Rating Scale (UPDRS) motor score; other impairment scales used included the Webster Rating Scale and the Columbia University Rating Scale. Parkinsonian disability was mainly reported using the UPDRS activities of daily living (ADL) score, but the Schwab and England, and the Northwestern University Disability Scales were also used. We have used the UPDRS motor and UPDRS ADL scales in our analysis because these had the most data. Some trials reported mean final scores while others reported the mean change in scores from baseline. All trials measured patients while on treatment, and some studies also measured patients after a washout period. In addition, trials measured severity after different follow up durations. Assessment of impairment and disability data at follow up greater than one year was hampered by large losses to follow up. No study measured quality of life.

One study (PSG 1996) used different doses of lazabemide. There was no dose-response relationship and so we used the arithmetic mean of the impairment and disability scores and their standard deviations across the four treatment doses.

Mean change in UPDRS motor score from baseline to one year on treatment (comparison 1.2)

For parkinsonian impairment we analysed change in UPDRS motor scores from baseline to one year. Data from five studies (1262 patients, 52% of all patients and 88% of patients randomized in those five trials) were available for this analysis. One other study also reported UPDRS motor scores (Swedish PSG 1998) but losses

ro follow up ar one year (61%) were too high to allow inclusion in the meta-analysis. Inclusion of this trial, however, did not alrer the results.

All the studies reporting this outcome favoured treatment with MAO-B inhibitors. The weighted mean difference (WMD) was -3.81 (95% CI -5.36 to -2.27). This result shows that the mean decline in the motor impairment score at one year was nearly four points (out of a total scale of 108 points) less in participants treated with MAO-B inhibitors than in those treated with control. Although this result is highly statistically significant (P value < 0.00001) its clinical significance is unclear and the results should be treated with caution because we cannot be certain these data were normally distributed.

There was significant heterogeneity (I^2 54.3%) amongst the studies in this analysis. However, this heterogeneity was entirely attributable to the PSG 1996 study which used lazabemide. When this study was excluded from the analysis, the I^2 value was 0%. The results suggest that lazabemide (WMD -1.35; 95% CI -3.09 to 0.39) has a significantly weaker effect than selegiline (WMD - 4.55; 95% CI -5.62 to -3.47, P value 0.002).

UPDRS motor scores at one year follow up (comparison 1.3)

In addition to analysing the change in impairment scores over one year, we also looked at the actual scores at one year follow up. Only two studies reported data that we could use in this analysis (217 patients, 9% of all patients). Both studies favoured treatment with MAO-B inhibitors, the difference varied between -1.20 and -3.00. We did not carry out meta-analysis, however, because some data were skewed.

Mean change in UPDRS ADL score form baseline to one year (comparison 1.4)

Six studies reported UPDRS ADL scores but once again we omitted data from one study because of large losses to follow up (Swedish PSG 1998). Data from 1262 participants were available (52% of all patients, 88% of those randomized in the six studies). All the studies favoured treatment with MAO-B inhibitors. The WMD was -1.50 (95% CI -2.53 to -0.48, P value 0.004), that is the scores were about one and a half points better (out of a total score of 52 points) after one year in parients treated with MAO-B inhibitors. Again, we cannot discount the possibility that some of the disability data were skewed.

As with the impairment scores, there was an apparent difference in effect between the studies using selegiline (WMD -2.23; 95% CI -2.84 to -1.61) and the study that used lazabemide (WMD -0.47; 95% CI -1.31 to 0.37). This accounted for the substantial heterogeneity (I^2 59.1%) in this analysis. Subgroup analysis showed a highly significant difference between the two types of MAO-B inhibitor used (P value 0.0006).

UPDRS ADL scores at one year follow up (comparison 1.5)

Only two srudies reported this outcome (217 patients, 9% of all patients). Mera-analysis could nor be performed because some dara were skewed but there was no good evidence of significanr improvemenrs with MAO-B inhibirors.

Mean change in UPDRS total score from baseline to end of washout (comparison 1.6)

Six studies incorporated a washout period into the study design to minimise the effects of drug therapy on symproms compared wirh any effects on disease progression. Two studies (DATATOP 1993; Norway-Denmark 1999) reporred data on insufficient numbers of patients to allow inclusion in this analysis and one did not report the total UPDRS score (California 1989). Data from the other three studies (PSG 1996; Swedish PSG 1998; US 1995) were combined in meta-analysis with a total of 429 patients (18% of all patients, 74% of those included in the three studies). The mean duration of follow up (weighted for study size) for this analysis was 1.1 years. The length of the washout was between two weeks and two months. Meta-analysis yielded a weighted mean difference of -3.15 (95% CI -5.48 to -0.82, P value 0.008), that is the increase in severity score from baseline to the end of washout was about three points less in the treatment group. Heterogeneity was low (I^2 19.7%) and there was no obvious trend between the duration of the washout and result.

Levodopa requirements

Participants requiring levodopa (comparison 1.7)

All six studies in which MAO-B inhibitors were initially compared with control in the absence of levodopa reported the number of participants who subsequently required levodopa. Three studies (DATATOP 1993; PSG 1996; UK 1996) assessed this outcome at a comparable follow up period of about one year (1088 patients, 77% of patients in studies without levodopa from the beginning, 95% of those randomized in the three studies). The combined OR was 0.53 (95% CI 0.36 to 0.79), significantly in favour of MAO-B inhibitors (P value 0.01) and with no significant heterogeneity (I^2 29.5%). The absolute rate of requiring levodopa at one year varied in the control groups of the three trials from about 15% (UK 1996) to 60% (DATATOP 1993) whereas baseline severity in terms of the UPDRS were similar. This implies either different rates of progression in the three trials or, perhaps more likely, different thresholds for starting levodopa. The number needed to treat with MAO-B inhibitors to avoid one person requiring levodopa at one year, therefore, varied between 16 (95% CI 11 to 59) at a control event rare of 15% to 7 (95% CI 4 to 30) at a control rate of 60%. The California 1989 study reported these data at three years by which time only one patient (in the selegiline arm) did not require levodopa. In the other two studies all the patients were receiving levodopa at the end of about four years of follow up (Finland 1997; Swedish PSG 1998).

Time until levodopa was required (Table 1)

Five srudies reported this outcome (1288 patients, 91% of parients in trials without levodopa from the outset). Because the data from these studies were skewed it was not possible ro use formal meta-analysis. However, the data from all these studies showed a delay in the median time to introduce levodopa with MAO-B inhibitors of between 4.1 and 8.7 months.

Table 1. Time to levodopa

Study ID	Measure	MAOB inhibitor	Control
California 1989	Mean ± SD	548.9 ± 286.2 days	312.1 ± 208.6 days
DATATOP 1993	Median	719 days	454 days
Finland 1997	Median ± SE Mean ± SE	545 ± 90 days 686.7 ± 73.7 days	372 ± 28 days 487.0 ± 74.4 days
PSG 1996	Mean ± SE	310.2 ± 13.1 days	276 ± 15.7 days
SPSG 1999	Median ± quartile deviation	386.3 ± 276.8 days	261.6 ± 243.3 days

Mean levodopa dose (Table 2)

Data from five trials were available for this outcome. We could not calculate the total number of patients included in this analysis because one study (UK-PDRG 2001) did not report this figure. A meta-analysis was not done because the data were skewed and there was substantial heterogeneity. The latter was partly attributable to varying durations of follow up, ranging from one to four years. All these studies showed higher levodopa doses in the control groups than in patients treated with MAO-B inhibitors. The difference varied between 30 and 185 mg/day of levodopa and generally increased as the duration of follow up increased up to five years (Finland 1997; Norway-Denmark 1999; SELEDO 1999; UK-PDRG 2001).

Table 2. Daily levodopa dose (mean or median)

Study ID	Length of follow up	N (MAO-B inhibitor)	Dose (MAO-B inhib)	N (control)	Dose (control)	Difference
US 1995 (bromocriptine arms)	1 year	22	Mean 85 mg (SD 198)	19	Mean 117 mg (SD 173)	32 mg/day
US 1995 (levodopa arms)	1 year	20	Mean 382 mg (SD 155)	21	Mean 426 mg (SD 110)	44 mg/day
Finland 1997	About 3 years	23	Mean 358 mg (SD 117)	21	Mean 543 mg (SD 150)	185 mg/day
SELEDO 1999	About 3.5 years	26	Mean 338 mg	20	Mean 521 mg	183 mg/day
UK-PDRG 2001	4 years	Unknown	Median 375 mg	Unknown	Median 625 mg	250 mg/day

Table 2. **Daily levodopa dose (mean or median)** *(Continued)*

Norway-Denmark 1999	5 years	38	Mean 424 mg (SD 113)	43	Mean 506 mg (SD 184)	82 mg/day

Development of motor complications

Motor fluctuations (comparison 1.8)

Data from five trials (1319 patients, 54% of all patients, 80% of those randomized in the five trials) were available, all of which used selegiline. The mean weighted duration of follow up was 3.4 years. There were three issues that created some difficulty in analysing these data. Firstly, raw data from the UK-PDRG 2001 study did not show any difference in the number of patients developing motor fluctuations between the selegiline and non-selegiline arms at the end of followup (161 of 271 (59%) versus 146 of 249 (59%) respectively). However, the rate of developing motor fluctuations was lower in the selegiline arm (157.5 per 1,000 patient-years versus 179.7 per 1,000 patient-years), implying that the selegiline patients had longer follow up (mean 3.8 years versus 3.4 years). In the main analysis we adjusted for this difference although we also performed an analysis with the raw data. Secondly, owing to the changes in the study design over time, data on fluctuations from the DATATOP study did not include a substantial number of patients (36%); we felt justified in including DATATOP in the main analysis because the losses were similar in both arms of the study. However, we also performed an analysis excluding DATATOP. Thirdly, the definitions of motor fluctuations varied: two trials included "end of dose deterioration" (Finland 1997; Norway-Denmark 1999), one "severe end of dose deterioration and random on/off fluctuations" (SELEDO 1999), one "on/off fluctuations" (UK-PDRG 2001), and one "wearing off" (DATATOP 1993).

The overall effect was significantly in favour of MAO-B inhibitors (OR 0.75; 95% CI 0.59 to 0.94, P value 0.01) with no evidence of heterogeneity (I^2 0%). However, this result was very dependent on the adjusted results of the UK-PDRG study and if the unadjusted figures were used the overall result became non-significant (OR 0.86; 95% CI 0.68 to 1.08). Excluding the DATATOP study, increased the observed benefit with selegiline (OR 0.64; 95% CI 0.47 to 0.87).

The rate of developing fluctuations varied in the control groups from 16% to 68%. This variation may have been due to differences in definitions since the mean duration of follow up was very similar. The number needed to treat with selegiline to prevent one person developing motor fluctuations over about 3.5 years varied from 15 (95% CI 8 to 73) to 29 (95% CI 17 to 123) across these baseline risks.

Results were not reported for 336 patients in these five studies. We performed a modified worst-case analysis: excluded subjects in the treatment group were given the highest event rate in any individual study (164 of 240, 68%) whilst excluded patients in the control group were given the lowest in any individual study (7 of 61, 11%). This made the results non-significant (OR 1.02; 95% CI 0.53 to 1.95). A null study of 540 patients with an event rate of 46% would be required to make the motor fluctuations data non-significant.

The following subgroup analyses were also performed:

(1) there was no difference between high-quality trials and lower-quality trials: OR 0.74 versus 0.67, P value 0.78;

(2) there was no difference between trials which used levodopa at the beginning of the trial and trials which used MAO-B inhibitor alone from the outset: OR 0.65 versus 0.87, P value 0.29.

Dyskinesias (comparison 1.9)

Data on the incidence of dyskinesias were reported in only four trials (1228 participants, 51% of all randomized patients, 80% of those randomized in the four trials). The mean duration of follow up (adjusted for study size) was 3.5 years. Adjustments were again made to the data from the UK-PDRG study to account for the slightly shorter follow up in the control group. The result showed no difference between intervention and control (OR 0.98; 95% CI 0.76 to 1.26). As with the motor fluctuations data, re-analysis using the raw data from the UK-PDRG study did not alter the results (OR 0.99), nor did exclusion of the DATATOP trial which again had missing data for this outcome (OR 0.94).

Patients with adverse events (comparison 1.10)

Four trials (614 patients, 26% of all patients, 97% of those randomized in the four trials) reported the numbers of patients with any significant adverse events. The precise definitions probably varied between trials. Overall, there was a non-significant trend for more adverse events with MAO-B inhibitors (OR 1.38; 95% CI 0.92 to 2.06, P value 0.12). The reporting of individual side-effects (for example nausea, confusion, hallucinations, postural hypotension) varied significantly between trials, with many trials not

reporting any information on specific side-effects and others only reporting those that were significantly different between treatmenr groups. This introduced a reporting bias. Five studies (1203 patients, 50% of all patients) reported data on nausea (comparison 1.11). More patients in the MAO-B inhibitor group reported nausea but the overall difference was not significant (OR 1.64; 95% CI 0.85 to 3.17). Another study reported significantly higher rates of gastrointestinal side-effects (Swedish PSG 1998) and another study reported significantly higher withdrawals due to upper gastrointestinal side-effects (UK-PDRG 2001).

Concerns have been raised about potentially harmful cardiovascular side-effects of MAO-B inhibitors including postural hypotension and cardiac arrhythmias. However, the studies in this review that reported data on blood pressure (DATATOP 1993; Finland 1997; Swedish PSG 1998; UK 1996) did not find lower mean blood pressures in patients in the MAO-B arms. DATATOP 1993 reported significantly more arrhythmias with selegiline than with control (eight versus one); one other study reported more ECG abnormalities with selegiline (Norway-Denmark 1999); and one other study reported no difference in development of ECG abnormalities between lazabemide and control (PSG 1996). The arrhythmias that were reported were not considered life threatening.

Two studies reported significantly higher numbers of patients in the MAO-B inhibitor groups with elevated serum aminotransferases (DATATOP 1993; PSG 1996). However, these enzyme abnormalities were not thought to pose serious health risks. There was insufficient information reported to evaluate neuropsychiatric side-effects.

Withdrawals

Six trials (1226 patients, 51% of all patients randomized) reported the numbers of withdrawals due to adverse events at the end of follow up (comparison 1.12). There were significantly more withdrawals with MAO-B inhibitors (OR 2.36; 95% CI 1.32 to 4.20, P value 0.004) and with no significant heterogeneity (I^2 30%). The rate of withdrawal in the control group was generally about 10% implying that for every 10 patients treated there would be one extra withdrawal with MAO-B inhibirors. There were no significanr differences between high (OR 1.69) and low quality (OR 2.57) trials (P value 0.47); trials which used levodopa or a dopamine agonist from the beginning (OR 2.52) and trials which used MAO-B inhibirors alone from the outset (OR 1.98, P value 0.70); and trials using selegiline (OR 2.92) and lazabemide (OR 1.41, P value 0.29).

All 10 trials reported data on total numbers of withdrawals by end of follow up (comparison 1.13). Data were reported from 2318 participants, all patients except the re-randomized patients from the UK-PDRG study. We have included losses to follow up in the total number of withdrawals (losses to follow up were not consistently reported) but have nor included deaths. There was no significant difference in the numbers of withdrawals between the MAO-B inhibiror and control arms (OR 0.93; 95% CI 0.74 to 1.16).

DISCUSSION

Since most of the data in this review were from studies using selegiline our conclusions predominately relate to selegiline. Given that one of the aims of treatment of Parkinson's disease should be to reduce disability and mortality in the long term, it was disappointing that none of the trials assessed our primary outcome which was chosen to capture both of these factors. We feel that future studies should incorporate this clinically important outcome into the study design, particularly for trials of possible neuroprotective agents that would be expected to delay disability.

Death

There has been much debate about whether selegiline increases the risk of death after the finding that it was associated with excess mortality in the UK-PDRG trial. This present review of all the available randomized evidence showed no significant increase in death with MAO-B inhibitors in general or selegiline specifically. Although the confidence interval does not exclude a small increase in death, only the UK-PDRG trial has suggested an excess of deaths with selegiline; we feel that this was probably a chance finding. However, there is no doubt that there was a dramatic reduction in the prescription of selegiline (in the UK at least) following the publication of the UK study (Clarke 2001), which highlights the dangers of changing practice on the basis of a single trial's results. Whilst the confidence interval does not exclude an increase in death rates with MAO-B inhibitors it does exclude any significant reduction in mortality as was suggested by the observational data from the 1980s (Birkmayer 1985).

Disease progression, impairment and disability

Many claims and counter claims have been made with regard to the effect of MAO-B inhibitors on the progression of Patkinson's disease. Some neurologisrs have argued that MAO-B inhibitors confer a neuroprotective effect and so delay disease progression; other researchers have taken a more cautious approach and considered any beneficial effects of MAO-B inhibitors to be merely symptomaric improvements due to their dopaminergic effects. It is difficulr clinically to separate out a symptomatic effect from an effect on disease progression. One way is to assess outcome following the withdrawal of medication to try to remove any symptomaric effect. However, this requires precise information about the duration of a symptomatic effect, which is often lacking. Moreover, ir becomes difficult ro withdraw treatment for long periods of time in patients with Parkinson's disease who require treatment to control their symptoms. An alternative strategy to differentiate a symptomatic from a disease-modifying effect would be to establish whether differences in impairment and disability on treatment or

control medication diverge over time, as would be expected with a disease modifying effect; or whether they remain static, suggesting a symptomatic effect. However, this would require long term follow up over several years.

This review showed that MAO-B inhibitors did reduce impairment and disability in Parkinson's parients in the shorr term, both on treatment and after washout but the clinical significance of these benefits is less clear because the changes were small and the data limited both in terms of quantity and quality. As expected the trials used several different measures of impairment and disability, which made meta-analysis difficult, but there were also other data issues that hindered analysis. Trials reported the data in various ways (for example absolute scores or change in scores from baseline), in various states (that is on or off medication) and at various time points. In trials which used the introduction of levodopa as the primary outcome measure the timing of the assessment was not the same in the MAO-B inhibitor and control arms, which made changes in impairment difficult to interpret. Few trials were analysed on an intention-to-treat basis so patients who dropped out were not included in these analyses. Finally, it was often unclear whether the data were normally distributed, which can invalidate the statistical methods used for meta-analysis.

Due to these problems the most robust measures of impairment and disability in this review were changes in 'on treatment' motor and ADL UPDRS scores at one year. Even these should be interpreted cautiously for several reasons. We had to make certain assumptions about the data for several of the trials in calculating the standard deviations (see methods section); the analyses only included about 50% of all randomized patients; and, by definition, these outcomes give no information about any long-term effects, in particular whether differences diverged over time. Although both analyses showed highly statistically significant changes in favour of MAO-B inhibitors the clinical relevance of a four and one point difference in motor and disability scores respectively seems uncertain to say the least. There was limited indirect evidence that lazabemide was less effective than selegiline although to our knowledge no direct randomized comparisons have been performed.

Whilst the analysis of those studies that included a washout phase to minimise any symptomatic effects did show a significant benefit in favour of MAO-B inhibitors, we would caution against interpreting this as demonstrating a significant slowing of disease progression. This is for several reasons. Firstly, the absolure difference was small (about three points out of a total UPDRS score of 176, which combines moror, ADL and mentation components). Secondly, it was based on limired data (only 582 patients). And thirdly, it remains unclear whether the washout periods (a mean of 1.3 months) were long enough to ensure complete elimination of the study drug. Some researchers have suggested that a washout of rwo months may be insufficienr, citing a half-life of 40 days for selegiline (Fowler 1996). If this is correct some if not all of the residual effect of MAO-B inhibitors observed after washout could have been an ongoing symptomatic effect. We did not find any relationship between duration of washout and change in severity score but our data were only from four studies. Taken overall, our results from the impairment and disability scores do not provide any strong evidence for a delay in disease progression with MAO-B inhibitors.

Levodopa requirements

The reduction in levodopa requirements that we found at one year is consistent with a symptomatic effect of MAO-B inhibitors. However, as expected given the weak nature of this symptomatic effect, as the disease progressed over three to four years almost all patients eventually required levodopa. The exact duration of this levodopa sparing effect in any given patient may vary depending on several factors including how early in the disease MAO-B inhibitors are started. If treatment is started early when the symptoms are very mild levodopa may not be required for many months whilst if started later, when symptoms are more severe, levodopa may be required much sooner. What is more interesting is that once patients started levodopa the dose required in those taking MAO-B inhibitors remained significantly lower than for those who were not taking them and that this difference increased over time. Whether this implies a slowing in disease progression remains unclear as does the importance of minimising the levodopa dose in delaying long term complications (see below).

Motor complications

One of the most serious consequences associated with long-term levodopa use is the development of motor fluctuations and dyskinesias. Some data have shown that lower doses of levodopa are associated with a lower risk of these complications (Poewe 1986) and recent guidelines have recommended minimising the dose of levodopa because of this (Olanow 1998b; PDCWG 2001). However, it is likely that using lower levodopa doses reflects less severe striatonigral neurodegeneration and it may be that it is the latter that is the most important determinant of motor complications.

We found that as well as being associated with lower levodopa doses selegiline was associated with a 25% reduction in the odds of moror flucruations but no reduction in dyskinesias. There may be several reasons for this apparent discrepancy between these two types of motor complication. Firstly, the reduction in motor fluctuations may be spurious since it was based on a relatively small number of patients; was largely dependent on the result from the UK-PDRG trial which had to be adjusted for differences in the duration of follow up; and was not robust to sensitivity analysis based on losses ro follow up. However, a similar reduction in motor fluctuations was found in a study comparing selegiline with levodopa that was not eligible for this review (Italian PDSG 2001). Secondly, it may be that MAO-B inhibitors do also reduce dyskinesias and that the present result for dyskinesias is a false negative one. For

example, the lower confidence limit for dyskinesias is compatible with a 20% to 25% reduction in the odds of dyskinesias. Thirdly, it may be that the effect of MAO-B inhibitors on motor fluctuations is purely a symptomatic one rather than due to any fundamental effect on the mechanisms that cause motor complications. The earliest and most common motor fluctuation is end-of-dose wearing off. MAO-B inhibitors may reduce this by prolonging the dopamine half-life in the synapse but may not have any effect on more random on/off oscillations and dyskinesias. There is increasing clinical and experimental evidence to suggest that the latter are triggered by the intermittent stimulation of the striatal dopamine receptors (Katzenschlager 2002; Olanow 1998b) so that it may be that pulsatile exogenous dopamine, largely independent of the actual levodopa dose, is the main cause of these motor complications.

If the reduction in motor fluctuations with selegiline is real the next issue would be to determine whether it is clinically relevant. This is unclear from the data in this review as we were unable to determine the severity of the fluctuations.

Safety

In general the side-effects reported by patients receiving MAO-B inhibitors were mild and well tolerated. However, analyses were limited by incomplete and unstandardized reporting of specific side-effects. There were non-significant trends for more side-effects and, in particular, more nausea with MAO-B inhibitors. There were twice as many withdrawals due to adverse events with MAO-B inhibitors but not all of these were due to the medication. Although there may have been a greater incidence of cardiac arrhythmias and elevated hepatic enzymes these were rare and not thought to be life threatening. We were unable to assess whether there were more psychiatric complications with MAO-B inhibitors and could not confirm the higher risk of postural hypotension that some have found (Churchyard 1999). Given that we have not shown clear evidence of an increase in deaths with selegiline we believe that MAO-B inhibitors are safe in early Parkinson's disease.

AUTHORS' CONCLUSIONS

Implications for practice

We did not find any convincing evidence that MAO-B inhibitors significantly delay disease progression in early Parkinson's disease. Our data on parkinsonian impairment and disability scores were consistent with a small symptomatic effect but the clinical relevance of this was uncertain. Similarly, although there is good evidence that MAO-B inhibitors have a levodopa sparing effect, whether this results in fewer long term, clinically relevant motor complications is unclear; there are promising data on motor fluctuations. The existing data do not exclude the possibility that MAO-B inhibitors cause an increase in mortality but, given that only one trial has suggested this, we consider it very unlikely. Other side-effects were generally mild and infrequent. Overall we do not feel the present evidence supports the routine use of selegiline or any other MAO-B inhibitor in early Parkinson's disease although clinicians may wish to consider it in situations where they feel it is important to delay or limit levodopa exposure for example in young patients.

Implications for research

More research is required, particularly to determine:

1. whether selegiline or other MAO-B inhibitors do increase death rates. Further analysis of the existing data may help clarify this (for example survival analysis using hazard ratios rather than the crude counting of deaths at the end of follow up). We hope to perform such an analysis in a subsequent version of this review but it is likely that additional randomized data will be required;

2. whether the reduction in motor fluctuations is real, clinically relevant, and is also associated with a reduction in dyskinesias;

3. the relative benefits of the newer MAO-B inhibitors over selegiline.

A large ongoing trial of selegiline in early Parkinson's disease (PD MED, http://www.pdmed.bham.ac.uk/) will provide additional important data although it will not be eligible for this review since it compares initiating treatment with selegiline alone versus levodopa alone or dopamine agonists alone (that is it is not comparing selegiline with no selegiline). We believe that further trials in early Parkinson's disease comparing the combination of MAO-B inhibitors with either levodopa or dopamine agonists versus monotherapy with levodopa or agonists alone are merited.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

California 1989

Methods	G: "biased coin" C: no details given Patients/doctors/assessors blind W: 5 in selegiline group (1 excluded, 2 lost to FU); 5 in placebo group (2 excluded) Not ITT
Participants	California, USA 54 randomized 27 to selegiline; 27 to placebo Incl: untreated idiopathic PD or treatment < 1 yr, H&Y I/II, duration < 5 yrs Excl: age <30 or >80; major medical or psychiatric disorders, dementia Baseline mean UPDRS (motor): selegiline 22; placebo 21
Interventions	Treatment: selegiline 5 mg twice a day Control: Placebo Duration of treatment: up to 3 years (mean 312 days in selegiline group; 549 days in placebo group)
Outcomes	Deaths UPDRS H&Y S&E Time to levodopa Withdrawals due to side-effects Total withdrawals
Notes	Mean FU: selegiline 0.9 yrs placebo 1.5 yrs 1 month washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

DATATOP 1993

Methods	G: computer C: central allocation 2x2 factorial design Patients/doctors/assessors blind W (before primary endpoint): 27 in selegiline group; 30 in placebo group ITT for deaths only

DATATOP 1993 *(Continued)*

Participants	USA 800 randomized 399 to selegiline; 401 to placebo Incl: untreated idiopathic PD not requiring symptomatic treatment at present, H&Y I / II, duration < 5 yrs Excl: age <30 or > 79, dementia, severe tremor, certain drugs, unstable medical or psychiatric problems, previous neurosurgery Baseline mean UPDRS: selegiline 25; placebo 25
Interventions	Treatment: selegiline 10 mg daily Control: placebo Also tocopherol
Outcomes	Deaths UPDRS Time to levodopa Motor fluctuations Dyskinesias Total withdrawals
Notes	Mean FU: 8.2 yrs 2 month washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Finland 1997

Methods	G: computer C: sealed envelopes Patients/doctors/assessors blind W: 15 in selegiline group; 5 in placebo group Not ITT
Participants	Finland 56 randomized 28 to selegiline; 28 to placebo Incl: untreated idiopathic PD, H&Y I - III Excl: other neurological diseases, active psychosis, severe medical diseases Baseline mean WRS: selegiline 8; placebo 8
Interventions	Treatment: selegiline 10 mg daily Control: placebo Levodopa combination therapy in phase II of study

Finland 1997 *(Continued)*

Outcomes	Deaths WRS CURS NUDS Time to levodopa Mean levodopa dose Motor fluctuations Withdrawals due to side-effects Total withdrawals
Notes	Mean FU: selegiline 6.0 yrs ; placebo 5.7 yrs No washout No significant differences in blood pressure found

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Norway-Denmark 1999

Methods	G: unknown C: central allocation Patients/doctors/assessors blind W: 28 in selegiline group; 24 in placebo group Not ITT
Participants	Norway and Denmark 163 randomized 77 to selegiline; 86 to placebo Incl: untreated idiopathic PD or levodopa < 6 months, H&Y I - III Excl: age <35 or >75, dementia, psychosis, unstable diseases Baseline mean UPDRS: selegiline 37; placebo 35
Interventions	Treatment: selegiline 10 mg daily Control: placebo Both groups also received levodopa Duration of treatment: up to 5 years
Outcomes	Deaths UPDRS Mean levodopa dose Motor fluctuations Withdrawals due to side-effects Total withdrawals

Norway-Denmark 1999 (*Continued)*

Notes	Mean FU: selegiline 2.9 yrs; placebo 3.1 yrs 1 month washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

PSG 1996

Methods	G: unknown C: unknown 5 group parallel study Patients/doctors/assessors blind W: 34 in lazabemide group, 13 in placebo group ITT for primary outcome only
Participants	USA 321 randomized 60 to 25 mg group, 67 to 50 mg group, 64 to 100 mg group, 64 to 200 mg group, 66 to placebo Incl: untreated idiopathic PD, H&Y I / II, <7 yrs duration Excl: severe tremor, unstable medical or psychiatric problems, dementia Baseline mean UPDRS: 25 mg group 23; 50 mg group 23; 100 mg group 21; 200 mg group 21; placebo 20
Interventions	Treatment: lazabemide 12.5 / 25 / 50 / 100 twice a day Control: placebo Duration of treatment: 52-54 weeks
Outcomes	Deaths UPDRS Levodopa requirement Total withdrawals
Notes	FU: 56 weeks 2-4 week washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

SELEDO 1999

Methods	G: unknown C: unknown Patients/doctors/assessors blind W: 35 in selegiline group; 35 in placebo group Not ITT
Participants	Germany 116 randomized 61 to selegiline; 55 to placebo Incl: untreated idiopathic PD or levodopa < 1 yr, H&Y I - III Excl: age >75, dementia, serious concomitant diseases, certain drugs Baseline mean CURS: selegiline 23; placebo 26
Interventions	Treatment: selegiline 5 mg twice a day Control: placebo Both groups also received levodopa Duration of treatment: up to 5 years
Outcomes	Deaths Withdrawals due to side-effects Total withdrawals
Notes	Mean FU: selegiline 3.9 yrs ; placebo 3.6 yrs No washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Swedish PSG 1998

Methods	G: unknown C: unknown Patients/doctors/assessors blind W: 9 in selegiline group; 7 in placebo group Not ITT
Participants	Sweden 157 randomized 81 to selegiline; 76 to placebo Incl: untreated idiopathic PD, H&Y I-III Excl: unstable medical or psychiatric diseases; age > 75 Baseline mean UPDRS selegiline 24; placebo 21
Interventions	Treatment: selegiline 10 mg daily Control: placebo Median duration of treatment: 12.7 months in selegiline arm; 8.6 months placebo arm

Swedish PSG 1998 *(Continued)*

Outcomes	Deaths UPDRS Time to levodopa requirement Total withdrawals
Notes	Median FU: selegiline 14.7 months; placebo 10.6 months 2 month washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

UK 1996

Methods	G: unknown C: unknown Patients/doctors/assessors blind W: 1 in selegiline group; 4 in placebo group Not ITT
Participants	UK 30 randomized 14 to selegiline; 16 to placebo Incl: untreated idiopathic PD, H&Y I - III Excl: age < 65, Mental or physical disorders affecting performance or evaluation, medication with effect on CNS Baseline median H&Y: selegiline 2; placebo 2
Interventions	Treatment: selegiline 5 mg twice a day Control: placebo Duration of treatment and FU: 54 weeks
Outcomes	Deaths Levodopa requirements Total withdrawals
Notes	FU: 54 weeks No washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

UK-PDRG (RR) 1998

Methods	G: random number tables C: central allocation Patients/doctors/assessors all unblinded ITT
Participants	UK 104 patients from arm 3 re-randomised 51 to selegiline; 53 to control Incl and excl criteria as for UK-PDRG 2001
Interventions	Treatment: selegiline 5 mg twice a day Control: no selegiline Both groups received levodopa
Outcomes	Deaths
Notes	Patients who initially could not tolerate bromocriptine were subsequently re-randomized to selegiline or no selegiline Mean duration of FU: 6.8 years No washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

UK-PDRG 2001

Methods	G: random number tables C: central allocation 3 parallel groups Patients/doctors/assessors all unblinded W: 123 in selegiline group (4 lost to mortality FU); 129 in placebo group (6 lost to mortality FU) ITT
Participants	UK 520 randomized 271 to selegiline; 249 to control (also bromocriptine arm) Incl: untreated idiopathic PD with incapacity requiring dopaminergic treatment Excl: Dementia, previously failed to respond to dopaminergic drugs Baseline mean WRS: selegiline 11; control 11
Interventions	Treatment: selegiline 5 mg twice a day Control: no selegiline Both groups received levodopa Mean mortality FU: 9.2 years

Outcomes	Deaths WRS Mean levodopa dose Motor fluctuations Dyskinesias Withdrawals due to side-effects Total withdrawals
Notes	Mean FU: 9.2 yrs No washout

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

US 1995

Methods	G: computer C: unknown 2x2 factorial design Patients/doctors/assessors blind W: 10 in selegiline group; 9 in placebo group Not ITT
Participants	US 101 randomized 52 to selegiline; 49 to placebo Incl: untreated idiopathic PD, H&Y stage I - III, Excl: previous neurosurgery, clinically significant medical or laboratory abnormalities Baseline mean UPDRS: selegiline 25; placebo 21
Interventions	Treatment: selegiline 10mg daily Control: placebo Half also received levodopa (sinemet) and half received bromocriptine (doses adjusted as clinically appropriate) Duration of treatment: 12 months
Outcomes	Deaths UPDRS Mean levodopa dose Total withdrawals
Notes	FU: 14 months 2 month washout

Risk of bias

US 1995 *(Continued)*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

G = generation of sequence; C = concealment of randomization; W = withdrawals; ITT = intention-to-treat analysis; Incl = inclusion criteria; Excl = exclusion criteria;
FU = follow up; PD = Parkinson's disease; yr = year
H&Y = Hoehn and Yahr stage; CURS = Columbia University Rating Scale; NUDS = Northwestern University Disability Scale; S&E = Schwab and England scale
UPDRS = Unified Parkinson's Disease Rating Scale; WRS = Webster Rating Scale

Characteristics of excluded studies *[ordered by study ID]*

Dalrymple-Alford 95	Too short - 8 weeks duration
FSMT 1993	Too short - 3 months duration
Haapaniemi 2000	Confounded - selegiline versus levodopa versus bromocripitine Too short - 6 months treatment
Italian PDSG 2001	Confounded - selegiline versus levodopa versus dopamine agonist
Mally 1995	Too short - 3 weeks duration
Nappi 1991	Too short - 6 months duration
PSG Lazabemide 1994	Too short - 8 weeks duration
PSG Rasagiline 2004	Too short - rasagiline versus no rasagiline for 6 months
RSG 2000	Too short - 12 weeks duration; some patients late disease
Stern 2004	Too short - 10 weeks duration
TEMPO 2002	Too short - 26 weeks duration

DATA AND ANALYSES

Comparison 1. Monoamine oxidase B inhibitors versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths at end of follow up (FU)	11	2389	Odds Ratio (M-H, Random, 95% CI)	1.15 [0.92, 1.44]
1.1 Selegiline - levodopa from outset	5	926	Odds Ratio (M-H, Random, 95% CI)	1.34 [0.99, 1.82]
1.2 Selegiline - no levodopa at outset	6	1142	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.71, 1.39]
1.3 Lazabemide - no levodopa at outset	1	321	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.09, 2.85]
2 Parkinsonian impairment - mean change in UPDRS motor score from baseline to 1 year	5	1262	Mean Difference (IV, Random, 95% CI)	-3.81 [-5.36, -2.27]
2.1 Selegiline - levodopa from outset	2	176	Mean Difference (IV, Random, 95% CI)	-4.12 [-6.58, -1.65]
2.2 Selegiline - no levodopa at outset	3	767	Mean Difference (IV, Random, 95% CI)	-4.65 [-5.85, -3.45]
2.3 Lazabemide - no levodopa at outset	1	319	Mean Difference (IV, Random, 95% CI)	-1.35 [-3.09, 0.39]
3 Parkinsonian impairment - UPDRS motor scores at 1 year FU	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Selegiline - levodopa from outset	2		Mean Difference (IV, Random, 95% CI)	Not estimable
3.2 Selegiline - no levodopa at outset	1		Mean Difference (IV, Random, 95% CI)	Not estimable
4 Parkinsonian disability - mean change in UPDRS ADL score from baseline to 1 year	5	1262	Mean Difference (IV, Random, 95% CI)	-1.50 [-2.53, -0.48]
4.1 Selegiline - levodopa from outset	2	176	Mean Difference (IV, Random, 95% CI)	-1.54 [-3.77, 0.68]
4.2 Selegiline - no levodopa at outset	3	767	Mean Difference (IV, Random, 95% CI)	-2.28 [-2.92, -1.65]
4.3 Lazabemide - no levodopa at outset	1	319	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.31, 0.37]
5 Parkinsonian disability - UPDRS ADL scores at 1 year FU	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Selegiline - levodopa from outset	2		Mean Difference (IV, Random, 95% CI)	Not estimable
5.2 Selegiline - no levodopa at outset	1		Mean Difference (IV, Random, 95% CI)	Not estimable
6 Mean change in UPDRS total score from baseline to end of washout	3	429	Mean Difference (IV, Random, 95% CI)	-3.15 [-5.48, -0.82]
6.1 Selegiline	2	223	Mean Difference (IV, Random, 95% CI)	-4.00 [-6.49, -1.52]

6.2 Lazabemide	1	206	Mean Difference (IV, Random, 95% CI)	-1.12 [-4.95, 2.71]
7 Participants requiring levodopa	6		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Follow up about 1 year	3	1088	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.36, 0.79]
7.2 At end of follow up	3	229	Odds Ratio (M-H, Random, 95% CI)	0.32 [0.01, 8.25]
8 Development of motor fluctuations	5	1319	Odds Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.94]
8.1 Selegiline - levodopa from outset	3	761	Odds Ratio (M-H, Random, 95% CI)	0.65 [0.48, 0.89]
8.2 Selegiline - no levodopa at outset	2	558	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.56, 1.36]
9 Development of dyskinesias	4	1228	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.76, 1.26]
9.1 Selegiline - levodopa from outset	2	662	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.71, 1.34]
9.2 Selegiline - no levodopa at outset	2	566	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.65, 1.51]
10 Subjects with adverse events	4	614	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.92, 2.06]
10.1 Selegiline - levodopa from outset	2	263	Odds Ratio (M-H, Random, 95% CI)	1.52 [0.83, 2.78]
10.2 Selegiline - no levodopa at outset	1	30	Odds Ratio (M-H, Random, 95% CI)	0.33 [0.03, 3.64]
10.3 Lazabemide	1	321	Odds Ratio (M-H, Random, 95% CI)	1.37 [0.79, 2.39]
11 Nausea	6	1203	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.85, 3.17]
11.1 Selegiline - levodopa from outset	2	267	Odds Ratio (M-H, Random, 95% CI)	2.19 [0.83, 5.80]
11.2 Selegiline - no levodopa at outset	4	936	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.48, 3.31]
12 Withdrawals due to adverse events	6	1226	Odds Ratio (M-H, Random, 95% CI)	2.36 [1.32, 4.20]
12.1 Selegiline - levodopa from outset	3	799	Odds Ratio (M-H, Random, 95% CI)	2.52 [1.03, 6.14]
12.2 Selegiline - no levodopa at outset	2	106	Odds Ratio (M-H, Random, 95% CI)	2.50 [0.63, 10.00]
12.3 Lazabemide - no levodopa at outset	1	321	Odds Ratio (M-H, Random, 95% CI)	1.41 [0.40, 4.98]
13 Total withdrawals	10	2318	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.16]
13.1 Selegiline - levodopa from outset	4	848	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.66, 1.23]
13.2 Selegiline - no levodopa at outset	6	1149	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.76, 1.64]
13.3 Lazabemide - no levodopa at outset	1	321	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.30, 1.29]

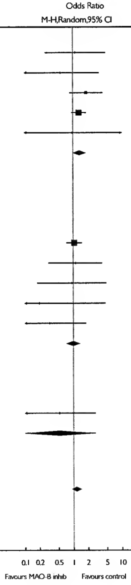
Analysis 1.1. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 1 Deaths at end of follow up (FU).

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 1 Deaths at end of follow up (FU)

Study or subgroup	MAO-B Inhibitor n/N	Control n/N	Odds Ratio M-H,Random,95% CI
1 Selegiline - levodopa from outset			
Norway-Denmark 1999	4/73	4/81	1.12 [0.27, 4.63]
SELEDO 1999	2/59	3/50	0.55 [0.09, 3.43]
UK-PDRG (RR) 1998	28/51	21/53	1.86 [0.85, 4.04]
UK-PDRG 2001	148/267	118/243	1.32 [0.93, 1.87]
US 1995	1/25	1/24	0.96 [0.06, 16.24]
Subtotal (95% CI)	**475**	**451**	**1.34 [0.99, 1.82]**
Total events: 183 (MAO-B Inhibitor), 147 (Control)			
Heterogeneity: Tau² = 0.0; Chi² = 1.71, df = 4 (P = 0.79); I² =0.0%			
Test for overall effect: Z = 1.88 (P = 0.060)			
2 Selegiline - no levodopa at outset			
California 1989	0/26	0/25	0.0 [0.0, 0.0]
DATATOP 1993	70/399	67/401	1.06 [0.73, 1.53]
Finland 1997	7/27	6/25	1.11 [0.31, 3.90]
Swedish PSG 1998	3/81	3/76	0.94 [0.18, 4.79]
UK 1996	0/14	2/16	0.20 [0.01, 4.54]
US 1995	2/27	5/25	0.32 [0.06, 1.83]
Subtotal (95% CI)	**574**	**568**	**0.99 [0.71, 1.39]**
Total events: 82 (MAO-B Inhibitor), 83 (Control)			
Heterogeneity: Tau² = 0.0; Chi² = 2.80, df = 4 (P = 0.59); I² =0.0%			
Test for overall effect: Z = 0.04 (P = 0.97)			
3 Lazabemide - no levodopa at outset			
PSG 1996	4/255	2/66	0.51 [0.09, 2.85]
Subtotal (95% CI)	**255**	**66**	**0.51 [0.09, 2.85]**
Total events: 4 (MAO-B Inhibitor), 2 (Control)			
Heterogeneity: not applicable			
Test for overall effect: Z = 0.77 (P = 0.44)			
Total (95% CI)	**1304**	**1085**	**1.15 [0.92, 1.44]**
Total events: 269 (MAO-B Inhibitor), 232 (Control)			
Heterogeneity: Tau² = 0.0; Chi² = 7.06, df = 10 (P = 0.72); I² =0.0%			
Test for overall effect: Z = 1.26 (P = 0.21)			



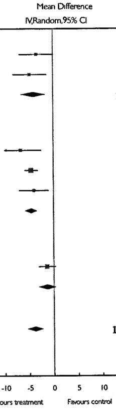
Analysis 1.2. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 2 Parkinsonian impairment - mean change in UPDRS motor score from baseline to 1 year.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 2 Parkinsonian impairment - mean change in UPDRS motor score from baseline to 1 year

Study or subgroup	MAO-B inhibitor N	Mean(SD)	Control N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 Selegiline - levodopa from outset						
Norway-Denmark 1999	62	-12.8 (10.9)	73	-9.4 (9.8)	12.3 %	-3.40 [-6.92, 0.12]
US 1995	20	-7 (6.3)	21	-2.2 (4.82)	12.6 %	-4.80 [-8.25, -1.35]
Subtotal (95% CI)	**82**		**94**		**24.9 %**	**-4.12 [-6.58, -1.65]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.31$, df = 1 (P = 0.58); $I^2 = 0.0\%$						
Test for overall effect: Z = 3.27 (P = 0.0011)						
2 Selegiline - no levodopa at outset						
California 1989	22	6.75 (4.92)	22	13.4 (8.54)	9.9 %	-6.65 [-10.77, -2.53]
DATATOP 1993	350	4.02 (8.29)	332	8.58 (9.88)	26.7 %	-4.56 [-5.93, -3.19]
US 1995	22	-3 (4.69)	19	1 (5.14)	14.7 %	-4.00 [-7.03, -0.97]
Subtotal (95% CI)	**394**		**373**		**51.4 %**	**-4.65 [-5.85, -3.45]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.10$, df = 2 (P = 0.58); $I^2 = 0.0\%$						
Test for overall effect: Z = 7.62 (P < 0.00001)						
3 Lazabemide - no levodopa at outset						
PSG 1996	253	3.95 (6.13)	66	5.3 (6.5)	23.7 %	-1.35 [-3.09, 0.39]
Subtotal (95% CI)	**253**		**66**		**23.7 %**	**-1.35 [-3.09, 0.39]**
Heterogeneity: not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						
Total (95% CI)	**729**		**533**		**100.0 %**	**-3.81 [-5.36, -2.27]**
Heterogeneity: $Tau^2 = 1.83$; $Chi^2 = 10.93$, df = 5 (P = 0.05); $I^2 = 54\%$						
Test for overall effect: Z = 4.84 (P < 0.00001)						



Analysis 1.3. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 3 Parkinsonian impairment - UPDRS motor scores at 1 year FU.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 3 Parkinsonian impairment - UPDRS motor scores at 1 year FU

Study or subgroup	MAO-B inhibitor N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI
1 Selegiline - levodopa from outset					
Norway-Denmark 1999	62	12.1 (9.9)	73	13.4 (9.4)	-1.30 [-4.57, 1.97]
US 1995	20	7.6 (5.81)	21	10.6 (5.04)	-3.00 [-6.34, 0.34]
2 Selegiline - no levodopa at outset					
US 1995	22	11.2 (4.69)	19	12.4 (4.36)	-1.20 [-3.97, 1.57]

-10 -5 0 5 10

Favours treatment Favours control

Analysis 1.4. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 4 Parkinsonian disability - mean change in UPDRS ADL score from baseline to 1 year.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 4 Parkinsonian disability - mean change in UPDRS ADL score from baseline to 1 year

Study or subgroup	MAO-B inhibitor N	Mean(SD)	Control N	Mean(SD)	Weight	Mean Difference IV,Random,95% CI
1 Selegiline - levodopa from outset						
Norway-Denmark 1999	62	-4.9 (13.4)	73	-3.8 (12.3)	4.8 %	-1.10 [-5.47, 3.27]
US 1995	20	-2.3 (4.71)	21	-0.6 (3.63)	11.0 %	-1.70 [-4.28, 0.88]
Subtotal (95% CI)	**82**		**94**		**15.8 %**	**-1.54 [-3.77, 0.68]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0.0\%$						
Test for overall effect: Z = 1.36 (P = 0.17)						
2 Selegiline - no levodopa at outset						
California 1989	22	2.69 (2.72)	22	4.45 (4.74)	13.0 %	-1.76 [-4.04, 0.52]
DATATOP 1993	350	1.58 (4.08)	332	3.97 (4.97)	31.2 %	-2.39 [-3.07, -1.71]

-10 -5 0 5 10

Favours treatment Favours control

(Continued . . .)

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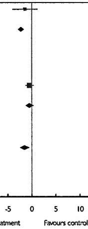
Study or subgroup	MAO-B inhibitor N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
US 1995	22	-1.5 (4.3)	19	-0.1 (4.15)		10.9 %	-1.40 [-3.99, 1.19]
Subtotal (95% CI)	**394**		**373**			**55.1 %**	**-2.28 [-2.92, -1.65]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.74$, df = 2 (P = 0.69); $I^2 = 0.0\%$							
Test for overall effect: Z = 7.04 (P < 0.00001)							
3 Lazabemide - no levodopa at outset							
PSG 1996	253	1.83 (3.05)	66	2.3 (3.1)		29.2 %	-0.47 [-1.31, 0.37]
Subtotal (95% CI)	**253**		**66**			**29.2 %**	**-0.47 [-1.31, 0.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.10 (P = 0.27)							
Total (95% CI)	**729**		**533**			**100.0 %**	**-1.50 [-2.53, -0.48]**
Heterogeneity: $Tau^2 = 0.76$; $Chi^2 = 12.21$, df = 5 (P = 0.03); $I^2 = 59\%$							
Test for overall effect: Z = 2.87 (P = 0.0041)							



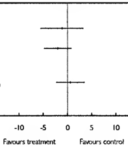
Analysis 1.5. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 5 Parkinsonian disability - UPDRS ADL scores at 1 year FU.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 5 Parkinsonian disability - UPDRS ADL scores at 1 year FU

Study or subgroup	MAO-B inhibitor N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Selegiline - levodopa from outset						
Norway-Denmark 1999	62	-4.9 (13.4)	73	-3.8 (12.3)		-1.10 [-5.47, 3.27]
US 1995	20	7.3 (4.92)	21	9.3 (4.12)		-2.00 [-4.78, 0.78]
2 Selegiline - no levodopa at outset						
US 1995	22	9.2 (4.69)	19	8.6 (4.79)		0.60 [-2.31, 3.51]



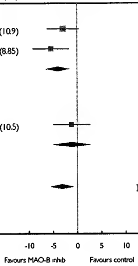
Analysis 1.6. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 6 Mean change in UPDRS total score from baseline to end of washout.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 6 Mean change in UPDRS total score from baseline to end of washout

Study or subgroup	MAO-B inhibitor N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Selegiline							
Swedish PSG 1998	72	11.3 (9.1)	69	14.2 (10.9)		38.1 %	-2.90 [-6.22, 0.42]
US 1995	42	0.4 (8.42)	40	5.8 (8.85)		31.5 %	-5.40 [-9.14, -1.66]
Subtotal (95% CI)	**114**		**109**			**69.6 %**	**-4.00 [-6.49, -1.52]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.96$, df = 1 (P = 0.33); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.16 (P = 0.0016)							
2 Lazabemide							
PSG 1996	172	7.58 (9.95)	34	8.7 (10.5)		30.4 %	-1.12 [-4.95, 2.71]
Subtotal (95% CI)	**172**		**34**			**30.4 %**	**-1.12 [-4.95, 2.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.57 (P = 0.57)							
Total (95% CI)	**286**		**143**			**100.0 %**	**-3.15 [-5.48, -0.82]**
Heterogeneity: $Tau^2 = 0.84$; $Chi^2 = 2.49$, df = 2 (P = 0.29); $I^2 = 20\%$							
Test for overall effect: Z = 2.65 (P = 0.0081)							



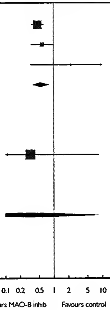
Analysis 1.7. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 7 Participants requiring levodopa.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 7 Participants requiring levodopa

Study or subgroup	MAO-B inhibitor n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 Follow up about 1 year				
DATATOP 1993	155/371	225/371		0.47 [0.35, 0.62]
PSG 1996	80/255	29/66		0.58 [0.34, 1.01]
UK 1996	4/13	2/12		2.22 [0.33, 15.18]
Subtotal (95% CI)	**639**	**449**		**0.53 [0.36, 0.79]**
Total events: 239 (MAO-B inhibitor), 256 (Control)				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 2.84$, df = 2 (P = 0.24); $I^2 = 30\%$				
Test for overall effect: Z = 3.18 (P = 0.0015)				
2 At end of follow up				
California 1989	21/22	22/22		0.32 [0.01, 8.25]
Finland 1997	23/23	21/21		0.0 [0.0, 0.0]
Swedish PSG 1998	72/72	69/69		0.0 [0.0, 0.0]
Subtotal (95% CI)	**117**	**112**		**0.32 [0.01, 8.25]**
Total events: 116 (MAO-B inhibitor), 112 (Control)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.0$, df = 0 (P = 1.00); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.69 (P = 0.49)				



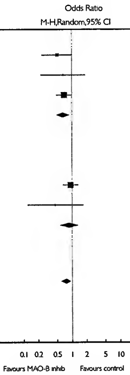
Analysis 1.8. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 8 Development of motor fluctuations.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 8 Development of motor fluctuations

Study or subgroup	MAO-B inhibitor n/N	Control n/N	Weight	Odds Ratio M-H,Random,95% CI
1 Selegiline - levodopa from outset				
Norway-Denmark 1999	17/65	30/72	10.5 %	0.50 [0.24, 1.02]
SELEDO 1999	7/61	9/55	4.9 %	0.66 [0.23, 1.92]
UK-PDRG 2001	161/268	164/240	41.1 %	0.70 [0.48, 1.01]
Subtotal (95% CI)	**394**	**367**	**56.4 %**	**0.65 [0.48, 0.89]**
Total events: 185 (MAO-B inhibitor), 203 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 0.68, df = 2 (P = 0.71); I² =0.0%				
Test for overall effect: Z = 2.69 (P = 0.0072)				
2 Selegiline - no levodopa at outset				
DATATOP 1993	88/273	81/241	40.5 %	0.94 [0.65, 1.36]
Finland 1997	5/23	8/21	3.1 %	0.45 [0.12, 1.70]
Subtotal (95% CI)	**296**	**262**	**43.6 %**	**0.87 [0.56, 1.36]**
Total events: 93 (MAO-B inhibitor), 89 (Control)				
Heterogeneity: Tau² = 0.02; Chi² = 1.09, df = 1 (P = 0.30); I² =8%				
Test for overall effect: Z = 0.62 (P = 0.53)				
Total (95% CI)	**690**	**629**	**100.0 %**	**0.75 [0.59, 0.94]**
Total events: 278 (MAO-B inhibitor), 292 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 3.46, df = 4 (P = 0.48); I² =0.0%				
Test for overall effect: Z = 2.44 (P = 0.015)				



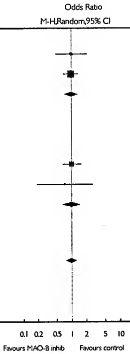
Analysis 1.9. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 9 Development of dyskinesias.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 9 Development of dyskinesias

Study or subgroup	MAO-B inhibitor n/N	Control n/N	Weight	Odds Ratio M-H,Random,95% CI
1 Selegiline - levodopa from outset				
Norway-Denmark 1999	18/73	20/81	11.9 %	1.00 [0.48, 2.08]
UK-PDRG 2001	150/268	136/240	51.9 %	0.97 [0.68, 1.38]
Subtotal (95% CI)	**341**	**321**	**63.8 %**	**0.98 [0.71, 1.34]**
Total events: 168 (MAO-B inhibitor), 156 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%				
Test for overall effect: Z = 0.14 (P = 0.89)				
2 Selegiline - no levodopa at outset				
DATATOP 1993	52/273	45/241	32.6 %	1.02 [0.66, 1.60]
Finland 1997	5/27	6/25	3.6 %	0.72 [0.19, 2.74]
Subtotal (95% CI)	**300**	**266**	**36.2 %**	**0.99 [0.65, 1.51]**
Total events: 57 (MAO-B inhibitor), 51 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.24, df = 1 (P = 0.62); I^2 =0.0%				
Test for overall effect: Z = 0.05 (P = 0.96)				
Total (95% CI)	**641**	**587**	**100.0 %**	**0.98 [0.76, 1.26]**
Total events: 225 (MAO-B inhibitor), 207 (Control)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.25, df = 3 (P = 0.97); I^2 =0.0%				
Test for overall effect: Z = 0.14 (P = 0.88)				



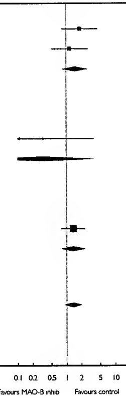
Analysis 1.10. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 10 Subjects with adverse events.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 10 Subjects with adverse events

Study or subgroup	MAO-B inhibitor n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Selegiline - levodopa from outset					
Norway-Denmark 1999	63/73	62/81		22.7 %	1.93 [0.83, 4.48]
SELEDO 1999	16/59	12/50		21.5 %	1.18 [0.50, 2.80]
Subtotal (95% CI)	**132**	**131**		**44.2 %**	**1.52 [0.83, 2.78]**
Total events: 79 (MAO-B inhibitor), 74 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.64, df = 1 (P = 0.42); I² =0.0%					
Test for overall effect: Z = 1.36 (P = 0.17)					
2 Selegiline - no levodopa at outset					
UK 1996	1/14	3/16		2.8 %	0.33 [0.03, 3.64]
Subtotal (95% CI)	**14**	**16**		**2.8 %**	**0.33 [0.03, 3.64]**
Total events: 1 (MAO-B inhibitor), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.90 (P = 0.37)					
3 Lazabemide					
PSG 1996	166/255	38/66		53.0 %	1.37 [0.79, 2.39]
Subtotal (95% CI)	**255**	**66**		**53.0 %**	**1.37 [0.79, 2.39]**
Total events: 166 (MAO-B inhibitor), 38 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.13 (P = 0.26)					
Total (95% CI)	**401**	**213**		**100.0 %**	**1.38 [0.92, 2.06]**
Total events: 246 (MAO-B inhibitor), 115 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 2.10, df = 3 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 1.57 (P = 0.12)					



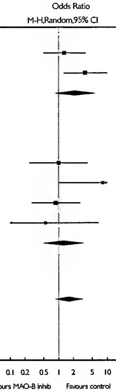
Analysis 1.11. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 11 Nausea.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 11 Nausea

Study or subgroup	MAO-B inhibitor n/N	Control n/N	Weight	Odds Ratio M-H,Random,95% CI
1 Selegiline - levodopa from outset				
Norway-Denmark 1999	9/77	8/89	24.3 %	1.34 [0.49, 3.66]
SELEDO 1999	20/56	6/45	24.0 %	3.61 [1.30, 10.00]
Subtotal (95% CI)	**133**	**134**	**48.3 %**	**2.19 [0.83, 5.80]**
Total events: 29 (MAO-B inhibitor), 14 (Control)				
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 1.85$, df = 1 (P = 0.17); $I^2 = 46\%$				
Test for overall effect: Z = 1.58 (P = 0.11)				
2 Selegiline - no levodopa at outset				
California 1989	5/27	5/27	16.3 %	1.00 [0.25, 3.95]
DATATOP 1993	8/399	1/401	8.5 %	8.18 [1.02, 65.74]
Finland 1997	9/27	9/25	20.8 %	0.89 [0.28, 2.79]
UK 1996	1/14	2/16	6.1 %	0.54 [0.04, 6.67]
Subtotal (95% CI)	**467**	**469**	**51.7 %**	**1.27 [0.48, 3.31]**
Total events: 23 (MAO-B inhibitor), 17 (Control)				
Heterogeneity: $Tau^2 = 0.28$; $Chi^2 = 4.19$, df = 3 (P = 0.24); $I^2 = 28\%$				
Test for overall effect: Z = 0.48 (P = 0.63)				
Total (95% CI)	**600**	**603**	**100.0 %**	**1.64 [0.85, 3.17]**
Total events: 52 (MAO-B inhibitor), 31 (Control)				
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 7.20$, df = 5 (P = 0.21); $I^2 = 31\%$				
Test for overall effect: Z = 1.47 (P = 0.14)				



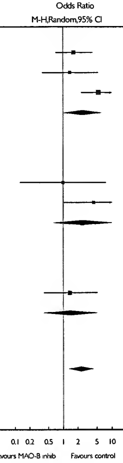
Analysis 1.12. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 12 Withdrawals due to adverse events.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 12 Withdrawals due to adverse events

Study or subgroup	MAO-B inhibitor n/N	Control n/N	Weight	Odds Ratio M-H,Random,95% CI
1 Selegiline - levodopa from outset				
Norway-Denmark 1999	14/77	10/86	24.6 %	1.69 [0.70, 4.06]
SELEDO 1999	6/61	4/55	14.3 %	1.39 [0.37, 5.21]
UK-PDRG 2001	37/271	7/249	26.2 %	5.47 [2.39, 12.51]
Subtotal (95% CI)	**409**	**390**	**65.1 %**	**2.52 [1.03, 6.14]**
Total events: 57 (MAO-B inhibitor), 21 (Control)				
Heterogeneity: Tau² = 0.37; Chi² = 4.94, df = 2 (P = 0.08); I² =59%				
Test for overall effect: Z = 2.03 (P = 0.043)				
2 Selegiline - no levodopa at outset				
California 1989	2/27	2/27	7.1 %	1.00 [0.13, 7.67]
Finland 1997	10/27	3/25	12.6 %	4.31 [1.03, 18.15]
Subtotal (95% CI)	**54**	**52**	**19.6 %**	**2.50 [0.63, 10.00]**
Total events: 12 (MAO-B inhibitor), 5 (Control)				
Heterogeneity: Tau² = 0.26; Chi² = 1.32, df = 1 (P = 0.25); I² =24%				
Test for overall effect: Z = 1.30 (P = 0.20)				
3 Lazabemide - no levodopa at outset				
PSG 1996	16/255	3/66	15.3 %	1.41 [0.40, 4.98]
Subtotal (95% CI)	**255**	**66**	**15.3 %**	**1.41 [0.40, 4.98]**
Total events: 16 (MAO-B inhibitor), 3 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.53 (P = 0.60)				
Total (95% CI)	**718**	**508**	**100.0 %**	**2.36 [1.32, 4.20]**
Total events: 85 (MAO-B inhibitor), 29 (Control)				
Heterogeneity: Tau² = 0.15; Chi² = 7.16, df = 5 (P = 0.21); I² =30%				
Test for overall effect: Z = 2.90 (P = 0.0037)				



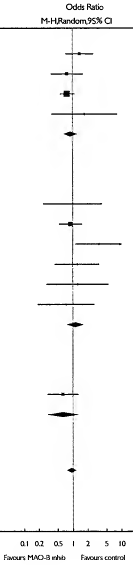
Analysis 1.13. Comparison 1 Monoamine oxidase B inhibitors versus control, Outcome 13 Total withdrawals.

Review: Monoamine oxidase B inhibitors for early Parkinson's disease

Comparison: 1 Monoamine oxidase B inhibitors versus control

Outcome: 13 Total withdrawals

Study or subgroup	MAO-B inhibitor n/N	Control n/N	Weight	Odds Ratio M-H,Random,95% CI
1 Selegiline - levodopa from outset				
Norway-Denmark 1999	28/77	25/86	11.2 %	1.39 [0.72, 2.69]
SELEDO 1999	35/61	35/55	8.8 %	0.77 [0.36, 1.63]
UK-PDRG 2001	123/271	129/249	36.2 %	0.77 [0.55, 1.09]
US 1995	5/25	3/24	2.1 %	1.75 [0.37, 8.30]
Subtotal (95% CI)	**434**	**414**	**58.2 %**	**0.90 [0.66, 1.23]**
Total events: 191 (MAO-B inhibitor), 192 (Control)				
Heterogeneity: Tau² = 0.01; Chi² = 3.30, df = 3 (P = 0.35); I² =9%				
Test for overall effect: Z = 0.67 (P = 0.51)				
2 Selegiline - no levodopa at outset				
California 1989	5/27	5/27	2.7 %	1.00 [0.25, 3.95]
DATATOP 1993	27/399	30/401	16.3 %	0.90 [0.52, 1.54]
Finland 1997	15/28	7/28	3.9 %	3.46 [1.12, 10.75]
Swedish PSG 1998	9/81	7/76	4.6 %	1.23 [0.43, 3.49]
UK 1996	6/14	6/16	2.3 %	1.25 [0.29, 5.41]
US 1995	5/27	6/25	2.8 %	0.72 [0.19, 2.74]
Subtotal (95% CI)	**576**	**573**	**32.6 %**	**1.11 [0.76, 1.64]**
Total events: 67 (MAO-B inhibitor), 61 (Control)				
Heterogeneity: Tau² = 0.0; Chi² = 4.96, df = 5 (P = 0.42); I² =0.0%				
Test for overall effect: Z = 0.54 (P = 0.59)				
3 Lazabemide - no levodopa at outset				
PSG 1996	31/255	12/66	9.2 %	0.62 [0.30, 1.29]
Subtotal (95% CI)	**255**	**66**	**9.2 %**	**0.62 [0.30, 1.29]**
Total events: 31 (MAO-B inhibitor), 12 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.27 (P = 0.20)				
Total (95% CI)	**1265**	**1053**	**100.0 %**	**0.93 [0.74, 1.16]**
Total events: 289 (MAO-B inhibitor), 265 (Control)				
Heterogeneity: Tau² = 0.01; Chi² = 10.37, df = 10 (P = 0.41); I² =4%				
Test for overall effect: Z = 0.64 (P = 0.52)				



APPENDICES

Appendix 1. The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1. PARKINSONIAN DISORDERS explode tree 1 (MeSH)
#2. parkinson*
#3. (#1 or #2)
#4. SELEGILINE single term (MeSH)
#5. MONOAMINE OXIDASE INHIBITORS single term (MeSH)
#6. selegiline
#7. deprenyl
#8. deprenil
#9. eldepryl
#10. jumex
#11. movergan
#12. rasagiline
#13. lazabemide
#14. (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)
#15. (#3 and #14)

Appendix 2. Medline search strategy

1. Parkinson$.tw.
2. exp Parkinsonian Disorders/
3. 1 or 2
4. Selegiline/
5. selegiline.tw.
6. deprenyl.tw.
7. eldepryl.tw.
8. jumex.tw.
9. movergan.tw.
10. rasagiline.tw.
11. lazabemide.tw.
12. or/4-11
13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized controlled trials/
16. random allocation/
17. double?blind method/
18. single?blind method/
19. clinical trial.pt.
20. exp clinical trials/
21. clin$ with trial$.tw.
22. placebos/
23. placebo$.tw.
24. random$.tw.
25. exp research design/
26. or/13-25
27. limit 26 to animal
28. limit 26 to human
29. 27 and 28
30. 27 not 29
31. 26 not 30
32. 3 and 12 and 31

Appendix 3. EMBASE search strategy

1. Parkinson Disease/
2. Parkinsonism/
3. Parkinson$.tw.
4. 1 or 2 or 3
5. Selegiline/
6. selegiline.tw.
7. deprenyl.tw.
8. eldepryl.tw.
9. jumex.tw.
10. movergan.tw.
11. rasagiline.tw.
12. lazabemide.tw.
13. or/5-12
14. clinical trial/
15. multicenter study/
16. phase 2 clinical trial/
17. phase 3 clinical trial/
18. phase 4 clinical trial/
19. randomized controlled trial/
20. controlled study/
21. meta analysis/
22. double blind procedure/
23. single blind procedure/
24. randomization/
25. major clinical study/
26. placebo/
27. drug comparison/
28. clinical study/
29. (clin$ adj25 trial$).tw.
30. ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
31. placebo$.tw.
32. random$.tw.
33. control$.tw.
34. or/14-33
35. human/
36. nonhuman/
37. 35 and 36
38. 36 not 37
39. 34 not 38
40. 4 and 13 and 39

WHAT'S NEW

Last assessed as up-to-date: 13 May 2005.

13 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2005

14 May 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Protocol: ADM, CEC, NI, RS.

Literature search: ADM, CEC, RS.

Literature selection: ADM, CEC.

Papers quality assessment: ADM, CEC.

Data collection from papers: ADM, CEC.

Interpretation of data: ADM, CEC, NI.

Review writing: ADM, CEC, NI, RS.

DECLARATIONS OF INTEREST

CC, NI, and RS are all either recruiting into or involved in running the PD MED trial.

SOURCES OF SUPPORT

Internal sources

- University of Aberdeen, UK.
- University of Birmingham, UK.

External sources

- The Health Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiparkinson Agents [therapeutic use]; Dopamine Agonists [therapeutic use]; Levodopa [therapeutic use]; Monoamine Oxidase Inhibitors [*therapeutic use]; Parkinson Disease [*drug therapy]; Picolinic Acids [therapeutic use]; Randomized Controlled Trials as Topic; Selegiline [therapeutic use]

MeSH check words

Humans

EXHIBIT B

Initiating Levodopa/Carbidopa Therapy With and Without Entacapone in Early Parkinson Disease

The STRIDE-PD Study

Fabrizio Stocchi, MD,[1] Olivier Rascol, MD,[2,3,4] Karl Kieburtz, MD,[5] Werner Poewe, MD,[6] Joseph Jankovic, MD,[7] Eduardo Tolosa, MD,[8] Paulo Barone, MD,[9] Anthony E. Lang, MD,[10] and C. Warren Olanow, MD[1,11]

Objective: L-dopa is the most widely used and most effective therapy for Parkinson disease (PD), but chronic treatment is associated with motor complications in the majority of patients. It has been hypothesized that providing more continuous delivery of L-dopa to the brain would reduce the risk of motor complications, and that this might be accomplished by combining L-dopa with entacapone, an inhibitor of catechol-O-methyltransferase, to extend its elimination half-life.

Methods: We performed a prospective 134-week double-blind trial comparing the risk of developing dyskinesia in 747 PD patients randomized to initiate L-dopa therapy with L-dopa/carbidopa (LC) or L-dopa/carbidopa/entacapone (LCE), administered 4× daily at 3.5-hour intervals. The primary endpoint was time to onset of dyskinesia.

Results: In comparison to LC, patients receiving LCE had a shorter time to onset of dyskinesia (hazard ratio, 1.29; $p = 0.04$) and increased frequency at week 134 (42% vs 32%; $p = 0.02$). These effects were more pronounced in patients receiving dopamine agonists at baseline. Time to wearing off and motor scores were not significantly different, but trended in favor of LCE treatment. Patients in the LCE group received greater L-dopa dose equivalents than LC-treated patients ($p < 0.001$).

Interpretation: Initiating L-dopa therapy with LCE failed to delay the time of onset or reduce the frequency of dyskinesia compared to LC. In fact, LCE was associated with a shorter time to onset and increased frequency of dyskinesia compared to LC. These results may reflect that the treatment protocol employed did not provide continuous L-dopa availability and the higher L-dopa dose equivalents in the LCE group.

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L-dopa is the most effective symptomatic therapy for Parkinson disease (PD). No other medical or surgical intervention has been shown to provide greater antiparkinsonian efficacy. However, chronic L-dopa therapy is associated with the development of potentially disabling motor complications, consisting of fluctuations in the motor response and involuntary movements or dyskinesias.[1–5]

The pathophysiologic basis of L-dopa–induced motor complications is not known, but current evidence sug-

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Additional Supporting Information can be found in the online version of this article.

TABLE 1: Consort Table: Patient Disposition

Disposition	LCE	LC	Total
Randomized[a]	373 (100)	372 (100)	745 (100)
Discontinued study treatment	108 (29.0)	96 (25.8)	204 (27.4)
Primary reason for discontinuation			
Adverse event(s)	38 (10.2)	24 (6.5)	62 (8.3)
Subject withdrew consent	37 (9.9)	24 (6.5)	61 (8.2)
Unsatisfactory therapeutic effect	14 (3.8)	33 (8.9)	47 (6.3)
Protocol violation	6 (1.6)	7 (1.9)	13 (1.7)
Lost to follow-up	6 (1.6)	4 (1.1)	10 (1.3)
Administrative problems	3 (0.8)	4 (1.1)	7 (0.9)
Death	3 (0.8)	0	3 (0.4)
No longer requires study drug	1 (0.3)	0	1 (0.1)
Completed Study	265 (71.0)	276 (74.2)	541 (72.6)

[a]Two randomized patients (1 in each group) did not receive study medication.
LCE = L-dopa/carbidopa/entacapone; LC = L-dopa/carbidopa.

gests that they may be related to nonphysiologic, discontinuous stimulation of striatal dopamine receptors.[6] Under normal circumstances, dopamine neurons in the substantia nigra pars compacta fire continuously, and striatal dopamine is maintained at a relatively constant level.[7–10] However, in PD, where there is degeneration of striatal dopamine terminals, striatal dopamine levels are dependent on peripheral L-dopa availability. As L-dopa has a relatively short half-life (60–90 minutes), intermittent doses do not restore striatal dopamine in a physiologic manner.[10,11] Rather, this pulsatile stimulation of dopamine receptors causes molecular changes in striatal neurons, physiologic changes in basal ganglia output neurons, and motor complications.[6] Nonetheless, L-dopa is routinely initiated with 2 to 3 daily doses, although there is no scientific basis for this treatment regimen. It has been proposed that more continuous delivery of L-dopa might be more physiologic and reduce the risk of motor complications; this concept is known as continuous dopamine stimulation (CDS). Indeed, continuous infusion of L-dopa has been shown to reduce both off time and dyskinesia in advanced PD patients.[12–17] Initiation of L-dopa in early PD with a strategy that provides more continuous availability of the drug might provide all of its benefits while reducing the risk of motor complications and avoiding the need for polypharmacy and surgical intervention. Surprisingly, there have been very few controlled studies evaluating how to initiate L-dopa. The ELLDOPA study demonstrated that higher doses of L-dopa are associated with greater symptomatic effects, but increased motor complications.[18] A controlled release formulation of L-dopa/carbidopa did not reduce the risk of dyskinesia compared with standard L-dopa,[19] but this formulation has variable absorption and is unlikely to have provided continuous L-dopa availability. Long-acting dopamine agonists are associated with a reduced risk of inducing motor complications,[20,21] but have less efficacy than L-dopa and are associated with other side effects such as psychosis and impulse control disorders.[22] Furthermore, nearly all dopamine agonist-treated patients eventually require L-dopa and develop dyskinesias at a rate similar to what is observed when L-dopa is initiated without dopamine agonists.[23,24] Thus, the development of a treatment strategy that provides the benefits of L-dopa with reduced motor complications remains among the major unmet medical needs in PD.

Inhibition of catechol-O-methyltransferase (COMT) blocks peripheral L-dopa metabolism and extends the elimination half-life of the drug.[25] In N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys, L-dopa combined with the COMT inhibitor entacapone administered 4× daily at 3.5-hour intervals provided enhanced motor responses with reduced dyskinesias in comparison to treatment with L-dopa alone.[26] In the present, we performed a double-blind trial comparing the risk of developing dyskinesia when patients with PD were initiated on L-dopa/carbidopa/entacapone (LCE) versus a standard formulation of L-dopa/carbidopa (LC) administered four times daily at 3.5 hour intervals.

TABLE 2: Baseline Demographics by Treatment (Intention to Treat Population)

Variable	LCE, n = 373	LC, n = 372	Total, N = 745
Age, mean yr	60.6 ± 8.7	59.8 ± 8.2	60.2 ± 8.4
Men, No. (%)	245 (65.7%)	222 (59.7%)	467 (62.7%)
Caucasian	352 (94.4%)	357 (96.0%)	709 (95.2%)
Weight, kg	79.7 ± 15.8	79.1 ± 16.9	79.4 ± 16.4
Mean duration of PD, yr	2.0 ± 1.6	2.0 ± 1.7	2.0 ± 1.7
UPDRS total (II + III)	32.7 ± 12.6	31.5 ± 11.9	32.1 ± 12.3
UPDRS, Part II (ADL)	9.6 ± 4.3	9.1 ± 4.2	9.4 ± 4.2
UPDRS, Part III (motor)	23.1 ± 9.5	22.4 ± 9.0	22.8 ± 9.3
Hoehn & Yahr stage	1.9 ± 0.5	1.9 ± 0.5	1.9 ± 0.5
Schwab & England score	86.4 ± 7.3	86.3 ± 8.6	86.4 ± 7.9
PDQ-39	25.2 ± 15.0	22.9 ± 13.7	24.1 ± 14.4
Previous antiparkinson medication, No. (%)	263 (70.5%)	266 (71.5%)	529 (71.0%)
Dopamine agonist use, No. (%)	217 (58.2%)	217 (58.3%)	434 (58.3%)

LCE = L-dopa/carbidopa/entacapone; LC = L-dopa/carbidopa; PD = Parkinson disease; UPDRS = Unified Parkinson Disease Rating Scale; ADL = activities of daily living; PDQ-39 = Parkinson Disease Questionnaire.

Patients and Methods

Subjects and Design

The STRIDE-PD (Stalevo Reduction In Dyskinesia Evaluation in Parkinson's Disease) study was a multicenter, double-blind study in patients with PD requiring the initiation of L-dopa therapy. Eligible subjects were men or women aged 30 to 70 years with a diagnosis of PD based on UK brain bank criteria and a disease duration of <5 years from time of diagnosis. Subjects could be taking stable doses of a dopamine agonist or other antiparkinsonian medications (no change in previous 4 weeks), but could not have taken amantadine within the preceding 270 days (due to its known antidyskinesia effects). Prior exposure to L-dopa for >30 days or within 8 weeks prior to entry, and previous use of a COMT inhibitor, were not permitted. Exclusion criteria included atypical or secondary parkinsonism, concomitant use of neuroleptic agents, prior neurosurgery for PD, and medical or psychiatric conditions that could interfere with the conduct of the study.

Subjects signed an institutional review board-approved informed consent and were randomized to receive treatment with identical capsules containing LC or LCE according to a centralized computer-generated randomization sequence. Treatment as-

TABLE 3: Baseline Demographics by Treatment and Dopamine Agonist Exposure (Intention to Treat Population)

Variable	DA Exposure at Baseline		No DA Exposure at Baseline	
	LCE, n = 217	LC, n = 217	LCE, n = 156	LC, n = 155
Age, mean yr	59.1	58.4	62.6	61.9
Men, No. (%)	151 (69.6)	132 (60.8)	94 (60.3)	90 (58.1)
Weight, mean kg	79.9	81.0	79.3	76.5
Duration of PD, mean yr	2.4	2.6	1.4	1.2
Hoehn & Yahr stage, mean	1.9	1.9	1.9	1.9
UPDRS Parts II + III, mean	33.0	31.1	32.2	32.2
UPDRS Part II, mean	9.7	9.2	9.4	9.0
UPDRS Part III, mean	23.3	21.9	22.8	23.2

DA = dopamine; LCE = L-dopa/carbidopa/entacapone; LC = L-dopa/carbidopa; PD = Parkinson disease; UPDRS = Unified Parkinson Disease Rating Scale.

signment was stratified by the use of dopamine agonists at baseline. L-dopa/carbidopa in both groups was initiated at a dose of 50/12.5mg twice daily, and titrated to 100/25 (target dose) or 150/37.5mg 4× daily administered at 3.5-hour intervals. For patients in the LCE group, entacapone 200mg was administered with each LC dose. If further treatment was required by patients in either group, an additional 50/12.5 or 100/25mg of open label LC could be added to each of the 4 study doses. No additional antiparkinsonian medication or change in dose of other antiparkinsonian medications was permitted during the course of the study. The study duration was 134 weeks; all subjects were followed blind until the last subject had completed the study. Visits were performed at baseline, weeks 1, 2, 6, 8, and 13, and at 13-week intervals thereafter. At each visit, a blinded treating investigator assessed the need for additional medication and performed safety assessments. Patients were also seen at each visit by a separate blinded rater who assessed for dyskinesia and performed the Unified Parkinson Disease Rating Scale (UPDRS) evaluation. Prior to study onset, all raters and patients were trained to identify dyskinesia.

Outcome Measures and Statistical Analysis

The primary endpoint was the time to onset of dyskinesia. Dyskinesia was determined by the blinded rater based on either direct observation or by patient response to specific questioning. Patients who did not have dyskinesia before discontinuing study medication were censored on the date of last dose of study medication. Kaplan-Meier curves with point-wise 95% confidence intervals (CIs) for the percentage of dyskinesia-free patients at each visit were provided. Analysis of time to onset of dyskinesia was performed in the intention-to-treat population using the 2-sided log-rank test stratified by dopamine agonist exposure at baseline and region at an alpha level of 5%. Time to dyskinesia was also evaluated using a definition of dyskinesia based only on direct observation or history. Predefined subgroup analysis based on dopamine agonist exposure at baseline was performed for the primary efficacy variable.

Secondary endpoints included frequency of dyskinesia, change from baseline in total UPDRS (Parts II and III), and time to, and frequency of, wearing-off episodes. UPDRS scores were analyzed using an analysis of covariance model with treatment, previous dopamine agonist exposure, region, and baseline score included as covariates in the model. Last observation carried forward was used to account for missing data. Incidence of dyskinesia and wearing off were analyzed using a logistic regression model with treatment group, duration of PD, region, and dopamine agonist exposure at baseline as factors in the model.

Safety variables were presented by treatment group using summary statistics. Following initiation of the study, the protocol was amended to assess the frequency of impulse control disorders such as pathological gambling, hypersexuality, and compulsive shopping in English-speaking patients in North America (LCE = 97, LC = 95) using the Modified Minnesota Impulsive Disorders Interview questionnaire.

Sample size calculations were based on previous trials indicating that L-dopa-induced dyskinesia occurs in approximately 30% of patients after 2 years of treatment.[20,21] With a follow-up time of 134 weeks and an estimated dropout rate of 15%, a sample size of 740 patients provided >80% power to detect a 25% reduction in dyskinesia frequency using the 2-sided log-rank test at an alpha level of 5%. All statistics are presented ± standard deviation unless otherwise specified.

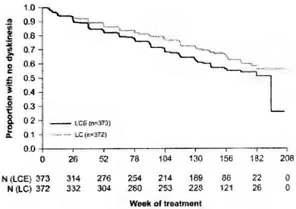

FIGURE 1: Kaplan-Meier survival curves show that patients randomized to L-dopa/carbidopa/entacapone (LCE) had greater risk of developing dyskinesia than patients receiving L-dopa/carbidopa (LC) (Cox proportional hazard ratio, 1.29; 95% confidence interval [CI], 1.0–1.65; p = 0.038). Survival time estimates for the first quartile of patients were 90.7 weeks (95% CI, 65.3–104.0) for the LCE group and 117.1 weeks (95% CI, 92.1–132.6) for LC-treated patients.

Results

A total of 747 patients from 77 centers in 14 countries in Europe and North America participated in the study. Enrollment required 74 weeks, so the maximum duration a subject was followed in the blinded phase was 208 weeks. Patient disposition and reasons for withdrawal are provided in Table 1. A total of 541 subjects (72.6%) completed their study drug treatment as planned; 265 (71.0%) in the LCE group and 276 (74.2%) in the LC group. Discontinuations due to adverse events and withdrawal of consent were higher in the LCE group, whereas discontinuation due to unsatisfactory therapeutic effect was higher in the LC group.

Baseline demographic data are provided in Tables 2 and 3. There were no significant differences between treatment groups. There was a slight imbalance of men in the LCE group, and LCE patients had slightly worse UPDRS and Parkinson Disease Questionnaire-39 scores. The groups were comparable with respect to the percentage of patients taking PD medications, and 58.3% of patients in each group were receiving a dopamine agonist. Patients on dopamine agonists were younger (58.7±8.6 vs 62.3± 7.8 years; $p < 0.001$), had longer disease duration (2.5±1.6 vs 1.3±1.5 years; $p < 0.001$), and were

TABLE 4: Dyskinesia by Treatment Group and by Subgroup

Variable	LCE, n = 373	LC, n = 372	p[a]
Dyskinesia Frequency by ITT Group			
Frequency [208 weeks], No. (%)	144 (38.6)	123 (33.1)	0.110
Survival time observed cases, mean wk	74.2 ± 47.9	79.1 ± 51.5	
Survival time observed cases, median wk	73.6	78.3	
Survival time observed cases Q1 estimates, wk (95% CI)	90.7 (65.3–104.0)	117.1 (92.1–132.6)	0.038
Disabling dyskinesia, No. (%)	32 (8.6)	23 (6.2)	0.201
Direct observation, No. (%)	130 (34.9)	110 (29.6)	0.118
Patient history, No. (%)	141 (37.8)	113 (30.4)	0.031
Direct observation or patient history on 2 consecutive visits, No. (%)	120 (32.2)	99 (26.6)	0.092
Direct observation on 2 consecutive visits, No. (%)	84 (22.5)	77 (20.7)	0.550
Frequency [134 weeks], No. (%)	128	103	0.016
Dyskinesia frequency by subgroup			
On dopamine agonist			
Frequency	91 ± 41.9	68 ± 31.3	
Time to onset, Q1 (95% CI)	78.9 (64.0,104.0)	117.4 (91.1,143.1)	0.006
Not on dopamine agonist			
Frequency	53 ± 34.0	55 ± 35.5	
Time to onset, Q1 (95% CI)	92.1 (65.1,129.9)	105.1 (82.1,143.0)	0.957
Age <65 yr, No./total (%)	102/223 (45.7)	95/253 (37.5)	0.021
Age ≥65 yr, No./total (%)	42/150 (28.0)	28/119 (23.5)	0.162
Men, No./total (%)	90/245 (36.7)	65/222 (29.3)	0.043
Women, No./total (%)	54/128 (42.2)	58/150 (38.7)	0.191
<75kg, No./total (%)	61/142 (43.0)	67/164 (40.9)	0.374
≥75kg, No./total (%)	83/231 (35.9)	56/208 (26.9)	0.018
Disease duration <2yr, No./total (%)	75/157 (47.8)	50/168 (29.8)	<0.001
Disease duration ≥2yr, No./total (%)	69/216 (31.9)	73/204 (35.8)	0.514
Without MAO-B inhibition, No./total (%)	123/335 (36.7)	115/343 (33.5)	0.170
With MAO-B inhibition, No./total (%)	21/38 (55.3)	8/29 (27.6)	0.005

[a]p values are post hoc, are not corrected, and are for descriptive purposes only.
LCE = L-dopa/carbidopa/entacapone; LC = L-dopa/carbidopa; ITT = intention to treat; CI = confidence interval; MAO-B = monoamine oxidase type B.

almost 5 years younger at time of disease onset than those not receiving a dopamine agonist.

Patients treated with LCE had an increased risk of developing dyskinesia compared to those receiving LC (hazard ratio, 1.29; p = 0.04). Kaplan-Meier curves showing survival rates with respect to remaining dyskinesia free are shown in Figure 1. The same results were seen when dyskinesia was defined based on direct observation alone, history alone, or presence on consecutive visits. Dyskinesia occurred more frequently in LCE patients through week 134 and week 208. Analyses by subgroup are provided in Table 4. Dyskinesias were more common in patients younger than 65 years, and LCE was associated with an increased risk of dyskinesia in younger, but not older, patients. Dyskinesias were more common in women than men, but LCE was more likely to induce

dyskinesia in men. Patients with lower body weight (<75kg) had more dyskinesia, but LCE was more likely to induce dyskinesia in heavier patients. Dyskinesias were more common in those with disease duration <2 years, and LCE was more likely to cause dyskinesia in those with a shorter duration of disease($p < 0.01$). Finally, patients receiving monoamine oxidase type B inhibitors were more likely to have dyskinesia than those who were not, and although numbers were small, had a much greater chance of having dyskinesia if they were receiving LCE ($p = 0.005$).

The analysis of the primary endpoint was repeated in the subgroup stratified for dopamine agonist exposure at baseline (Fig 2A and B). In patients receiving dopamine agonists, LCE-treated patients had a greater risk of dyskinesia (hazard ration, 1.55; $p = 0.006$), and a greater frequency of dyskinesia (41.9% vs 31.3%). However, there was no difference in the time to onset (hazard ratio, 0.99; 95% CI, 0.68–1.45; $p = 0.96$) or frequency (34% vs 35.5%) of dyskinesia between patients in the LCE and LC groups for those not receiving dopamine agonists.

Secondary endpoints are provided in Table 5. There was a trend to improved UPDRS scores in LCE-treated subjects (difference at final visit, 1.2 points; p = 0.1). The adjusted mean difference in change from baseline to final visit in UPDRS score between the LCE and LC groups was greater in those receiving concomitant dopamine agonists (difference, 1.8; $p = 0.08$) than in those who were not (difference, −0.1; $p = 0.95$). Wearing off occurred more frequently in LC than LCE patients (50.8% vs 44.2%; $p = 0.07$), but time to onset of wearing off was similar in the 2 groups. This result was not affected by use of dopamine agonists.

The mean L-dopa dose at the end of the titration period was 305.2 and 306.8mg/day in the LCE and LC groups, respectively, and they remained comparable throughout the study. However, pharmacokinetic studies show that the addition of entacapone causes a 1.32- to 1.39-fold increase in the plasma L-dopa area under the curve.[25] Accordingly, we calculated L-dopa dose equivalents by multiplying the L-dopa dose in LCE patients by 1.3. This analysis indicates that LCE-treated patients received significantly more L-dopa dose equivalents than LC patients at the completion of titration, at the time of onset of dyskinesia, and at the final study visit (see Table 5). Further, higher doses of L-dopa in both LC and LCE groups were associated with increased dyskinesias (26.4% of 375 patients receiving ≤400mg/day of L-dopa compared with 45.4% of 370 patients receiving >400mg/day; $p = 0.01$).

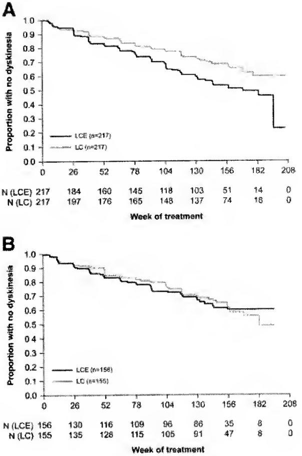

FIGURE 2: (A) Kaplan-Meier survival curves show that among patients who were receiving dopamine agonists at baseline, those randomized to L-dopa/carbidopa/entacapone (LCE) had greater risk of developing dyskinesia than those receiving L-dopa/carbidopa (LC) (Cox proportional hazard ratio, 1.55; 95% confidence interval [CI], 1.13–2.13; p = 0.006). The estimated first quartile time to onset of dyskinesia was 78.9 weeks for the LCE group and 117.4 weeks for LC. (B) Kaplan-Meier survival curves show that among patients who were not receiving dopamine agonists at baseline, those randomized to LCE did not have a greater risk of developing dyskinesia than those receiving LC (Cox proportional hazard ratio, 0.99; 95% CI, 0.68–1.45; p = 0.96).

Adverse events are provided in Table 6. LCE patients had an increased frequency of dopaminergic side effects (nausea, vomiting, and dyskinesia), as well as the anticipated increase in diarrhea and chromaturia. Myocardial infarction and prostate cancer were more common in LCE patients, and skin cancers were more common with LC. Three patients died while receiving study treatment (all LCE patients) due to metastatic lung adenocarcinoma, cardiac arrest, and pneumonia. Three patients died within 30 days of discontinuing treatment (LCE: 1 gastric cancer; LC: 1 malignant lung neoplasm, 1 chronic obstructive pulmonary disease). None of the deaths was consid-

TABLE 5: Secondary Endpoints (Intention to Treat Population)

Characteristic	LCE	LC	p^a
UPDRS II + III, Δ from BL to week 130	8.4	7.2	0.18
Wearing off			
Frequency [208 wks], No. (%)	165 (44.2%)	189 (50.8%)	0.07
Frequency [130 wks], No. (%)	139 (45.6%)	161 (48.3%)	0.53
Time to Wearing off, mean wk	72.9 ± 50.9	78.5 ± 51.5	0.53
Time to wearing off, Q1 estimate, wk	78.0	76.0	0.6
Time to wearing off, hazard ratio (95% CI)	0.94 (0.76–1.17)		
Hoehn & Yahr stage (Δ from BL)	0.4	0.3	NS
Schwab & England score (Δ from BL)	−1.4	−1.4	0.95
PDQ-39 (Δ from BL)	2.2	2.4	0.77
L-dopa dose equivalents			
End of titration	533.4	420.1	0.001
At onset of dyskinesia	659.9	535.2	0.001
At final study visit	524.1	432.6	0.001

[a]*p* values are post hoc, are not corrected, and are for descriptive purposes only.
LCE = L-dopa/carbidopa/entacapone; LC = L-dopa/carbidopa; UPDRS = Unified Parkinson Disease Rating Scale; BL = baseline; NS = not significant; PDQ-39 = Parkinson Disease Questionnaire.

ered to be related to the study drugs. Impulse control disorders were detected in 14 of 103 (13.6%) evaluable LCE patients and 15 of 102 (14.7%) evaluable LC patients (see Supplementary Table for further details). Of these, 12 LCE patients (85.7%) and 10 LC patients (66.7%) were receiving a dopamine agonist.

Discussion

The STRIDE-PD study failed to demonstrate that initiation of LCE in early PD patients was associated with a reduced frequency of dyskinesia in comparison to standard LC when administered 4× daily at 3.5-hour intervals. Indeed, LCE was associated with a shorter time to onset and increased frequency of dyskinesia. LCE showed a trend toward improved UPDRS scores and reduced wearing off compared to LC, consistent with the approved indication of entacapone as an adjunct to L-dopa.[27,28]

It is possible that LCE failed to demonstrate less dyskinesia than LC as had been hypothesized because the CDS theory is not correct. Alternatively, the dosing frequency of LCE employed in this trial may not have provided CDS. Indeed, twice daily administration of L-dopa with entacapone increased the risk of L-dopa–induced dyskinesias in MPTP-lesioned monkeys,[29] whereas dyskinesia frequency was reduced when the same dose was administered at more frequent intervals so as to presumably achieve CDS.[26] Pharmacokinetic studies demonstrate that the addition of entacapone to L-dopa administered 5× per day at 3-hour intervals avoids the low trough levels seen with standard LC in PD patients and provides more continuous L-dopa availability.[30] We nonetheless chose 4× daily administration at 3.5-hour intervals in this study because this dosing regimen was associated with reduced dyskinesias in MPTP-lesioned monkeys[26]; because we believed that the relative preservation of striatal dopamine terminals in early PD patients might provide a greater capacity to buffer fluctuations in L-dopa/dopamine concentration than in MPTP-lesioned monkeys, where there is more severe neurodegeneration, and because we believed that fewer doses would enhance the likelihood of compliance.[31] In retrospect, this may not have been a good decision, although there is no assurance that administering L-dopa 5× daily at 3-hour intervals would have been successful. Although the LCE dosing regimen chosen in this study failed to reduce dyskinesia, we believe that continued efforts to develop a long-acting oral formulation of L-dopa are worthwhile in an attempt to obtain the drug's benefits without motor complications.

We believe that the shorter time to onset and increased frequency of dyskinesia in the LCE group are likely due to the higher L-dopa dose equivalents administered in this group combined with a failure to achieve CDS. Indeed, LCE-treated patients had a higher fre-

TABLE 6: Number (%) of Patients with Most Frequent AEs (≥5% in any Treatment Group) and Other Important AEs[a]

AE	LCE, n = 373, No. (%)	LC, n = 371, No. (%)	Total, N = 744, No. (%)
Total No. of patients with an AE	348 (93.3)	336 (90.6)	684 (91.9)
Nausea	114 (30.6)	71 (19.1)	185 (24.9)
Diarrhea	66 (17.7)	28 (7.5)	94 (12.6)
Dizziness	59 (15.8)	46 (12.4)	105 (14.1)
Depression	58 (15.5)	51 (13.7)	109 (14.7)
Constipation	51 (13.7)	44 (11.9)	95 (12.8)
Back pain	47 (12.6)	54 (14.6)	101 (13.6)
Insomnia	47 (12.6)	53 (14.3)	100 (13.4)
Fatigue	40 (10.7)	42 (11.3)	82 (11.0)
Arthralgia	39 (10.5)	44 (11.9)	83 (11.2)
Pain in extremity	37 (9.9)	32 (8.6)	69 (9.3)
Somnolence	37 (9.9)	28 (7.5)	65 (8.7)
Anxiety	37 (9.9)	27 (7.3)	64 (8.6)
Headache	37 (9.9)	26 (7.0)	63 (8.5)
Nasopharyngitis	34 (9.1)	43 (11.6)	77 (10.3)
Fall	33 (8.8)	41 (11.1)	74 (9.9)
Edema peripheral	27 (7.2)	34 (9.2)	61 (8.2)
Abnormal dreams	25 (6.7)	17 (4.6)	42 (5.6)
Vomiting	22 (5.9)	10 (2.7)	32 (4.3)
Urinary tract infection	21 (5.6)	24 (6.5)	45 (6.0)
Dyskinesia	21 (5.6)	10 (2.7)	31 (4.2)
Bronchitis	20 (5.4)	21 (5.7)	41 (5.5)
Muscle spasms	20 (5.4)	21 (5.7)	41 (5.5)
Orthostatic hypotension	20 (5.4)	13 (3.5)	33 (4.4)
Hypertension	19 (5.1)	27 (7.3)	46 (6.2)
Upper respiratory tract infection	19 (5.1)	17 (4.6)	36 (4.8)
Musculoskeletal pain	19 (5.1)	16 (4.3)	35 (4.7)
Dry mouth	19 (5.1)	13 (3.5)	32 (4.3)
Dyspepsia	14 (3.8)	20 (5.4)	34 (4.6)
Rash	13 (3.5)	19 (5.1)	32 (4.3)
Tremor	11 (2.9)	26 (7.0)	37 (5.0)
Myocardial infarction	7 (1.9)	0 (0.0)	7 (0.9)
Prostate cancer	9 (2.4)	2 (0.5)	11 (1.5)
Skin cancer	7 (1.9)	12 (3.2)	19 (2.6)
Basal cell carcinoma	6 (1.6)	5 (1.3)	11 (1.5)
Squamous cell carcinoma	0	4 (1.1)	4 (0.5)
Melanoma	0	1 (0.3)	1 (0.1)

[a]AE where at least 1 was thought to be related to study treatment.
AE = adverse event.

quency of dopaminergic side effects, greater improvement in UPDRS scores, and less dropout for reason of lack of efficacy than LC-treated patients. These results are consistent with other trials demonstrating that higher doses of L-dopa are associated with an increased frequency of dyskinesia.[18]

Patients receiving dopamine agonists had a higher frequency of dyskinesias, and LCE was significantly more prone than LC to induce dyskinesias in this subpopulation. This is likely because patients on dopamine agonists were younger at baseline, were about 5 years younger at disease onset, had longer disease duration, and probably had greater disease severity as they had comparable baseline UPDRS scores despite receiving dopamine agonists. Increased dyskinesia in the LCE group on dopamine agonists might also relate to administration of greater L-dopa dose equivalents without achieving CDS, as the addition of entacapone has been shown to reduce the risk that L-dopa will induce dyskinesia in MPTP-lesioned monkeys receiving a dopamine agonist if CDS is achieved.[32] It is interesting that LCE did not increase the frequency or shorten the time to onset of dyskinesia in patients not on dopamine agonists, despite higher L-dopa dose equivalents, similar to what was observed in the FIRST-STEP study.[33] There is no obvious explanation for this, although patients not on dopamine agonists may have been less prone to develop dyskinesia in general because they were older, had shorter disease duration, and probably had less severe disease.

Adverse events of LC and LCE were similar to those seen in previous studies. Surprisingly, LCE was associated with increased myocardial infarction and prostate cancer, whereas LC was associated with increased skin cancer. This has not been observed in other clinical trials (although they have not been as long in duration) or in postapproval surveillance studies and are being further investigated.

There are important clinical implications of this study. STRIDE-PD does not support the early administration of L-dopa in combination with entacapone to reduce the risk of motor complications using the dosing regimen employed in this trial. This study did not, however, solve the problem of how to optimally administer L-dopa in early PD patients to prevent motor complications. Further studies will be required to assess whether the CDS hypothesis is valid, and whether more frequent LCE dosing at shorter time intervals or other longer-acting L-dopa preparations might provide superior results. The study confirms that higher doses of L-dopa are associated with an increased risk of dyskinesia, and supports careful L-dopa dose titration, using the lowest dose of L-dopa that provides satisfactory clinical control. In this regard, the availability of 50, 75 and 125, 150 mg LCE doses may prove of value in determining the optimal dose for individual patients in order to maximize efficacy while minimizing the risk of dyskinesia. However, the authors caution physicians against withholding the optimal L-dopa dose from patients who cannot be satisfactorily controlled with other medications.

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Authorship

F.S. and C.W.O. contributed equally to the study and to this article.

Potential Conflicts of Interest

The authors have each served as consultants to Novartis/Orion.

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EXHIBIT C

Movement Disorders
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Levodopa/Dopamine Replacement Strategies in Parkinson's Disease—Future Directions

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Abstract: After 40 years, levodopa remains the most effective therapy for the treatment of PD. However, long-term therapy is complicated by motor fluctuations and dyskinesia that can represent a source of significant disability for some patients. Other medical therapies that are currently available for the treatment of PD primarily represent an attempt to prevent or treat motor complications. Surgical therapies improve motor complications in appropriate candidates, but do not provide antiparkinsonian benefits that are superior to levodopa, and are themselves associated with potentially serious side effects. Increasing information suggests that levodopa-induced motor complications relate to pulsatile, nonphysiologic dopamine replacement. A therapeutic strategy that could deliver levodopa/dopamine to the brain in a more continuous and physiologic manner might be expected to provide all of the benefits of standard levodopa with reduced motor complications. Such a levodopa formulation might replace all current dopaminergic antiparkinsonian medications and avoid the need for surgery in most PD patients. However, problems of continuous dopaminergic stimulation must be addressed and avoided, and the issue of nondopaminergic features remains to be addressed. © 2008 Movement Disorder Society
Key words: levodopa; Parkinson's disease; motor complications

Levodopa has been the most effective symptomatic therapy for the treatment of Parkinson's disease (PD) since its introduction in the late 1960s, and remains the standard against which new interventions must be compared. While levodopa does not improve many features of PD such as freezing, falling, or dementia which probably reflect degeneration of nondopaminergic neurons, the drug has provided benefits to literally millions of patients. Almost all PD patients demonstrate a positive response to levodopa and experience less disability, improved quality of life, prolonged employability, and a reduced mortality rate. However, chronic treatment with levodopa is associated with the development of motor complications (motor fluctuations and dyskinesias) in the majority of cases.[1] Indeed, the recent ELLDOPA study demonstrated that initiation of levodopa 200 mg tid to previously untreated PD patients resulted in dyskinesias in 16% and wearing off in 20% after just 9 months of treatment.[2] No other currently available medical or surgical therapy for PD has been shown to provide symptomatic benefits that are superior to levodopa. Rather, they are primarily used to delay the introduction of levodopa (so as to delay the development of motor complications) or to reduce the severity of existing motor complications. The development of a levodopa formulation that did not induce motor complications would be a major advance in the treatment of PD.

In routine practice, levodopa is administered in combination with a decarboxylase inhibitor to prevent acute side effects such as nausea, vomiting, and orthostatic hypotension caused by the peripheral conversion of levodopa to dopamine with activation of dopamine receptors in the area postrema that are not protected by

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the blood brain barrier. Much less is known about how best to administer levodopa in order to avoid motor complications. Retrospective community-based studies suggest that levodopa-induced motor complications are associated with the administration of high levodopa doses, and are more common in young onset PD patients.[3,4] Few prospective or controlled studies have been performed to determine how to best employ levodopa. The ELLDOPA study, performed almost 40 years after initial reports of levodopa efficacy, was the first double-blind, placebo-controlled study to confirm that higher doses of levodopa are associated with enhanced efficacy but a greater risk of motor complications.[2] Disease severity also appears to play a role in determining the likelihood that motor complications will occur. Levodopa is much more likely to induce dyskinesias in fully lesioned marmosets compared with partially lesioned animals,[5] and much higher doses are required to induce dyskinesia in normal animals.[6] Similar findings have been observed in PD patients where chronic levodopa treatment does not induce motor complications in healthy individuals,[7] and where dyskinesias develop after a relatively short latency in patients with severe PD.[8] Several dopamine agonists have shown a reduced tendency to induce dyskinesia, but these drugs are not as effective as levodopa and patients eventually require levodopa treatment which increases the risk of developing motor complications.[9,10] Interestingly, recent reports indicate that the time to onset of motor complications after introducing levodopa is the same regardless of whether the drug is used as initial therapy or as an adjunct to a dopamine agonist.[11,12] Similarly, levodopa induces comparable dyskinesias in MPTP monkeys who are drug naïve or who are receiving stable doses of a dopamine agonist.[13] Thus, while agonists delay the time until levodopa is required, the introduction of levodopa leads to an increased risk of motor complications even when coadministered with a dopamine agonist.

The precise mechanism responsible for why levodopa is so dyskinesiogenic is not known, but increasing information suggests that it may relate to replacement of dopamine in a nonphysiological manner. A body of evidence indicates that in the normal condition, striatal dopamine levels are maintained at a relatively constant, level and that administration of levodopa in a discontinuous or "pulsatile" manner induces molecular changes in stratial neurons, and neurophysiologic changes in pallidal output neurons which lead to the development of motor complications.[14] Studies in both animal models and PD patients have shown that delivery of dopaminergic agents in a more continuous manner to try to mirror the physiologic state reduces the risk of developing motor complications.[15] These observations have formed the basis for the concept of Continuous Dopaminergic Stimulation (CDS) as a treatment strategy for PD. Based on this concept, many neurologists now initiate PD therapy with a long-acting dopamine agonist so as to delay the introduction of levodopa.[16] However, as noted earlier, PD patients eventually require levodopa therapy, and levodopa is prone to induce motor complications even in the presence of a dopamine agonist. This review will consider how levodopa might be administered in order to minimize the risk that it will induce motor complications.

TARGET STRATEGY FOR LEVODOPA ADMINISTRATION

Most physicians initiate carbidopa/levodopa at a dose of 25/100 mg two or three times daily. This is largely based on anecdotal experience, presumably aimed at finding the lowest dose of the drug that provides satisfactory clinical control. This approach does not, however, take into account what is known about the organization of the basal ganglia or attempt to replace dopamine in a physiologic manner. Indeed, there is almost no data to indicate that this is the correct or optimal way to administer levodopa.

There are considerable data available suggesting that under normal circumstances numerous mechanisms are in place to maintain dopamine levels in the striatum at a relatively constant level, and to provide relatively continuous activation of striatal dopamine receptors.[14] It is now appreciated that dopamine neurons in the substantia nigra pars compacta (SNc) fire both tonically and phasically.[17,18] SNc neurons normally fire continuously (tonically) in a random manner, independent of movement. This provides a relatively constant release of dopamine which primarily activates extrasynaptic dopamine D1 receptors on striatal medium spiny neurons which facilitate normal movement. Dopamine released by tonic firing diffuses from the synapse to reach these receptors by way of volume transmission, further ensuring relatively continous dopamine receptor activation. Dopamine neurons also fire phasically, bursting in response to anticipation of reward or exposure to novel stimuli.[19] Burst firing releases larger quanta of dopamine with activation of D1 and D2 receptors located primarily within the synapse. However, dopamine neurons that burst fire typically express large numbers of dopamine transporters which permit rapid and robust reuptake of dopamine from the synapse.[20] These mechanisms serve to maintain striatal and synaptic dopamine concentrations at a relatively constant level.[21,22]

Dopamine normally modulates glutamate-mediated excitability of medium spiny striatal neurons in both up and down directions, and selectively "filters" the massive glutamate input extending from cortex to striatum (an estimated 10,000 inputs per neuron), presumably to permit optimized firing for a desired movement.[23,24] Dopamine is also essential for modulating glutamate-mediated long-term potentiation (LTP) and depression (LTD) which enable selection of desired motor responses.[25] These effects are facilitated by the fact that dopamine receptors on striatal medium spiny neurons are closely linked anatomically to cortico-striatal glutamate receptors.[23] Postsynaptically, D1 receptor activation excites striato-pallidal neurons in the direct pathway (which inhibit pallidal outlow), while D2 receptor activation inhibits activity in striatal neurons comprising the indirect pathway which ultimately result in excitation of the pallidum.[26] Through these mechanisms, dopamine serves to stabilize the basal ganglia network and facilitate normal movement. There is considerable reserve in this system so that substantial dopamine denervation must occur before there is any impairment in normal motor function.

In PD, dopamine denervation leads to major changes in the basal ganglia system. There is a marked reduction in the number and size of dendrites on medium spiny neurons[27] with selective reduction in glutamatergic synapses.[28] There are also altered basal ganglia regulatory mechanisms with reduced modulation of the glutamatergic effects on medium spiny neurons[29] and impairment in LTP and LTD formation.[30] In addition, there are major changes in the firing pattern of basal ganglia output neurons (including but not limited to frequency) that are associated with the development of parkinsonian motor features.[31]

Traditional dosing with standard formulations of levodopa does not replace striatal dopamine in a physiologic manner and does not restore basal ganglia function to normal. With the degeneration of dopamine neurons and loss of buffering capacity of dopamine terminals, striatal dopamine levels become increasingly dependent on the peripheral availability of levodopa. Levodopa has a relatively short half life (60–90 min), and intermittent doses produce fluctuating plasma levels. This in turn leads to large oscillations in striatal and synaptic dopamine levels resulting in striatal dopamine receptors being alternately exposed to pathologically high or low levels of dopamine.[32,33] This discontinuous or "pulsatile" stimulation is associated with a series of gene changes in striatal neurons, alterations in the firing patterns of pallidal output neurons, and the development of motor complications. Indeed, it is likely that stimulation or lesions of the subthalamic nucleus (STN) or inner portion of the globus pallidus (GPI) reduce dyskinesia by eliminating these altered neuronal firing patterns which are presumably transmitting misinformation to cortical and brain stem motor areas. The current state of understanding of the molecular and physiologic mechanisms that underlie levodopa-induced motor complications are reviewed in articles by Obeso, Calabresi, and Grace.[25]

The observation that motor complications are associated with fluctuating striatal dopamine levels and intermittent activation of striatal dopamine receptors has led to the therapeutic concept of CDS. Here, it is hypothesized that dopaminergic therapies that are delivered in a continuous manner might provide more continuous activation of dopamine receptors, and thereby avoid the sequence of events leading to motor complications. In the laboratory, intermittent doses of short-acting dopaminergic agents such as levodopa are more likely to induce dyskinesias in MPTP-treated monkeys than are long-acting dopaminergic agents.[34,35] More importantly, studies in MPTP monkeys show that continuous administration of a short-acting dopaminergic agent induces significantly less dyskinesia than intermittent administration of the same agent.[36,37] Clinical trials in PD patients show similar results. In untreated PD patients, long-acting dopamine agonists are less likely to induce motor complications than short-acting formulations of levodopa.[9,10] In advanced PD patients, continuous administration of a dopamine agonist (e.g. apomorphine, lisuride) is associated with a reduction in both "off" time and dyskinesia in comparison with intermittent doses of standard levodopa.[38,39] Indeed, continuous infusion of levodopa significantly reduces both off time and dyskinesia in comparison with intermittent oral doses of the same drug.[40] These observations demonstrate the role of pulsatile stimulation in the origin of motor complications, independent of the dyskinesiogenic potential or receptor activation profile of a given dopaminergic molecule. With respect to levodopa which virtually all patients eventually require, the CDS concept suggests that if the drug could be administered in a more continuous manner, it might provide the same clinical benefits but with a reduced risk of inducing motor complications.

ATTEMPTS TO DELIVER LEVODOPA TO THE STRIATUM IN A MORE CONTINUOUS MANNER (TABLE 1)

Levodopa Infusion

One way to achieve continuous delivery of levodopa to the brain is to administer the drug by continuous

TABLE 1. *Possible approaches to provide more continuous delivery of levodopa/dopamine to the striatum*

Levodopa infusion
Levodopa patch
Levodopa rod
Cell-based therapies
Fetal nigral transplantation
Retinal pigmented epithelial cells
Stem cells
Trophic factors
Gene delivery approaches
AADC ± TH
Trophic factors (neurturin, GDNF)
Alternate formulations of levodopa
Levodopa CR formulations
Levodopa + a COMT inhibitor
Levodopa methyl ester
Levodopa prodrugs

infusion. In advanced PD patients, many studies have shown a reduction in "off" time and/or dyskinesia with continuous intraintestinal or intravenous infusion of levodopa.[41–44] Collectively, these studies serve as a proof of the concept that CDS can be applied to levodopa. However, levodopa infusion requires delivery of large volumes of fluid to be delivered because of the acidic nature of the drug required to maintain it in solution. This results in infusion systems which are large and cumbersome for the patient. To reduce the size of the infusion system to something more akin to an insulin pump, studies have utilized methylester levodopa which is more soluble and required less volume. Continuous intraintestinal infusion of methylester levodopa was associated with highly significant reductions in both "off" time and dyskinesia in comparison to oral administration of standard levodopa, and mean "on" time without dyskinesia increased from 0.3 ± 0.5 hours at baseline to 9.4 ± 0.8 hours at 6 months.[40] These benefits persisted during 4 years of follow-up. Another attempt to reduce the volume of the infusate involves the use of a methylcellulose gel which contains up to 20 mg of levodopa and 5 mg of carbidopa per ml (the Duodopa System). Continuous intraintestinal administration of duodopa provided similar benefits with respect to both off time and dyskinesia.[45,46] The Duodopa System is currently being tested in the United States, and is already available in some European countries. Benefits reported with levodopa infusion are of the same magnitude as have been reported with DBS, and may represent an alternative to intracranial surgery in advanced PD patients, particularly if there are cognitive problems. However, levodopa infusion still necessitates an operation for catheter placement, catheter revisions are frequently required, and infusions are still somewhat inconvenient. Further, no studies have examined levodopa infusion as a means of trying to prevent motor complications in animal models or in early PD patients, and it is unlikely that patients with mild disease that can be well controlled with regular levodopa would be willing to tolerate an infusion system.

Transdermal Delivery of Levodopa

A levodopa patch has long been considered as a way to provide continuous transdermal delivery of levodopa, but has proven difficult to achieve. Patches provide one means for providing continuous transdermal delivery of a drug, but for a patch to work the drug should ideally be effective in small concentrations, lipophilic, and relatively nonirritating to the skin. However, levodopa is maintained in an acidic concentration (to maintain its stability and prevent its undergoing oxidation) and requires large volumes for administration as indicated earlier. As a consequence, it has proven difficult to develop a viable levodopa patch. Levodopa methyl ethyl ester may be more suitable than standard levodopa for patch delivery because it requires less volume, but has not yet been shown to be stable and satisfactory for patch technology. Inhibition of fatty acid and sphingosine synthesis has been shown to enhance transdermal delivery of levodopa.[47] In rat, administration of cerulenin (a fatty acid synthesis inhibitor) increased levodopa absorption through the skin by threefold, and this effect was enhanced by coadministration of calcium chloride which modulates the duration of epidermal perturbation.[48] Transdermal delivery of the zwitterionic levodopa has been attempted using iontophoresis and ion-exchange fibers to stabilize levodopa and control drug delivery.[49] Another approach that has been tried utilizes two separate layers of L-dopa separated by a hydrogel sheet composed of cutaneous absorption enhancers, water, and ethanol. This approach has been shown to provide short-term levodopa stability and transdermal absorption in the rat.[50] None of these approaches has yet been demonstrated to be feasible for PD patients.

Polymer rods that can be implanted subcutaneously have been shown to be able to deliver drugs continuously for prolonged periods of time. In one study, continuous delivery of apomorphine via a subcutaneously implanted polymer rod provided continuous plasma levels and motor benefits in MPTP primates for 6 months.[37] Interestingly, these animals did not develop dyskinesia in contrast to control animals treated with standard intermittent injections of apomorphine. While this technology is fascinating and offers great promise, it is not likely to be useful for administering levodopa

because of the large daily dose that is required and the limited storage capacity of the rods.

Cell-Based Therapies

Cell-based therapies have been studied based on the assumption that implanted cells can manufacture dopamine, integrate into the host nigrostriatal system, and compensate for the degeneration of dopamine neurons that occurs in PD. It can be hypothesized that implanted dopamine cells that integrate into the host striatum might release dopamine and restore dopamine in a more physiologic manner than can be accomplished with oral levodopa. In the laboratory, fetal nigral transplants have been shown to survive, reinnervate the striatum, restore dopamine, self-regulate, and improve motor function in 6-OHDA lesioned rodents and MPTP monkeys.[51] In PD patients, implanted fetal nigral mesencephalic neurons have been shown to survive, to reinnervate the striatum in an organotypic manner, and to restore dopaminergic function on PET.[52] However, two double-blind controlled studies failed to demonstrate significant clinical benefit in comparison to placebo, and in both studies transplantation was associated with off-medication dyskinesias that persisted even following withdrawal of levodopa.[53,54] Post hoc analyses suggest that transplantation in patients who are young, have mild disease, and have a good response to levodopa, coupled with more prolonged use of immunosuppressants might lead to enhanced results,[55] but such studies have not yet been performed. Recent studies showing that implanted mesencephalic dopamine neurons contain lewy bodies and have reduced staining for dopamine transporter further dampens enthusiasm for this approach.[56]

Transplantation of fetal nigral porcine cells were reported to provide benefits for some patients in open label studies,[57] but these were not confirmed in a double-blind trial which has not yet been formally reported. Transplantation of retinal pigmented epithelial (RPE) cells attached to microcarriers (Spheramine®) has also been tested in patients with advanced PD. RPE cells manufacture levodopa and possibly trophic factors[58] and are thought to be relatively resistant to immune-mediated damage because of their separation from the vasculature. Motor benefits without dyskinesias have been reported in an open-label trial in PD patients,[59] and a double-blind controlled study is currently underway.

Stem cells have generated considerable enthusiasm because they offer a means of generating large numbers of optimized dopamine neurons for transplantation.[60] Ideally, stem cells could be induced to specifically differentiate into A9 nigrostriatal neurons that might integrate into the host striatum in a more normal manner than can be accomplished with mesencephalic transplants, in which only about 5% of cells are dopaminergic neurons and only a portion of which are directed to the dorsal striatum. Preliminary studies have focused on embryonic stem cells and benefits in the 6-OHDA lesioned rat and MPTP-treated monkey.[61,62] However, only relatively small numbers of implanted dopamine nerve cells derived from stem cells survive, and it remains to be established if such treatments can be effective and free of long-term complications such as tumor formation and off-medication dyskinesias. The potential for autologous stem cells derived from umbilical matrix, bone marrow, or skin to differentiate into dopamine neurons is currently being explored as is the possibility of using stem cells to deliver trophic factors.[63] Clinical trials in PD patients have not yet been performed with stem cells.

Gene Therapies and Trophic Factors

An alternate way to enhance dopaminergic function in the basal ganglia utilizes gene delivery technology. One approach involves using the AAV2 viral vector to deliver aromatic amino acid decarboxylase (AADC) ± tyrosine hydroxylase. This approach is based on the concept that enhanced expression of AADC would promote the conversion of orally administered levodopa to dopamine and provide more continuous striatal dopamine availability.[64] Positive results have been observed in MPTP monkeys,[65] and an open label clinical trial has been initiated in PD patients. Other groups have tried to enhance dopaminergic function with trophic factors. These are postulated to protect and/or restore dopamine neuronal function so as to enhance striatal dopamine availability and avoid pulsatile stimulation and motor complications. Glial-derived neurotrophic factor (GDNF) has been shown to protect dopamine neurons from a variety of toxins in both in vitro and in vivo models. Most strikingly, GDNF restores function to MPTP-treated monkeys even when administered after exposure to the toxin,[66] consistent with the molecule having a restorative effect on injured nerve cells. Open-label studies reported benefits of direct catheter infusion of GDNF into the striatum of PD patients.[67] However, a double-blind trial failed to show significant improvement with this technique, although significant benefits were observed on PET.[68] One of the limitations of catheter administration of GDNF could be that point-source delivery does not provide sufficient distribution of the protein to the striatum to permit a posi-

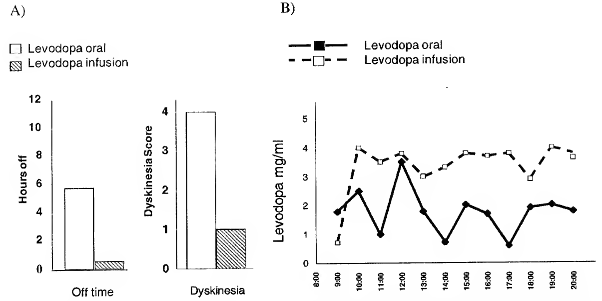

FIG. 1. A) Comparison of effect of levodopa on off time and dyskinesia when administered as intermittent standard oral doses or as a continuous infusion. Note that continuous infusion is associated with a significant reduction in both off time and dyskinesia. B) Comparison of plasma levodopa levels when the drug is administered by repeated doses of a standard oral formulation or by continuous infusion. Note that low plasma levodopa trough levels seen with intermittent oral delivery are largely avoided with continuous infusion.

tive clinical response. Gene delivery offers an opportunity to provide more diffuse distribution of the protein throughout the target region. Indeed lentivirus provided diffuse delivery of GDNF throughout the striatum in MPTP-lesioned monkeys, and was associated with strikingly positive behavioral, imaging, and histologic effects.[69] Similar results were observed in MPTP monkeys with AAV2 delivery of neurturin, a trophic factor in the GDNF family.[70–72] Based on these preclinical results, an open-label trial of AAV2-Neurturin injected into the striatum was performed in 12 advanced PD patients. In this study, gene delivery of neurturin resulted in significant improvement in UPDRS motor scores during practically defined off and reduced dyskinesia.[73] Based on these promising results, a double-blind, placebo-controlled trial has been initiated.

Novel Formulations of Levodopa

Strong theoretical and clinical evidence supports the notion that more continuous delivery of a levodopa preparation would reduce the risk of motor complications in PD. The use of infusion, cell-based therapies, or gene delivery, all have the potential to accomplish this goal, but it would clearly be preferable to provide continuous levodopa delivery with an oral or transdermal treatment strategy, especially if this approach is to be used in early PD patients. To facilitate achieving this goal, we defined the levodopa plasma pharmacokinetic (PK) profile in advanced PD patients who were receiving oral levodopa and experiencing severe "off" time and dyskinesias and the plasma PK profile in these same patients after they had received 6 months of continuous levodopa infusion and had experienced a significant reduction in both "off" time and dyskinesias.[40] As expected, intermittent doses of standard levodopa induced a pulsatile PK profile with high peak and low trough concentrations, whereas levodopa infusion provided relatively stable plasma concentrations and avoided low trough levels (Fig. 1). As plasma levodopa levels are thought to reflect striatal dopamine levels in the dopamine denervated state, the low plasma trough levels seen with oral doses of standard levodopa were interpreted to reflect low striatal dopamine levels and periods when striatal dopamine receptors would not be activated. It was hypothesized that an oral levodopa treatment strategy that provided a PK profile similar to that obtained with infusion should be able to provide comparable benefits. We therefore sought to replicate the levodopa PK profile with a variety of levodopa treatment strategies. We could not replicate this pattern with multiple doses of levodopa administered at 1–5-hour intervals, or with multiple dose combinations of a continuous release formulation of levodopa/carbidopa (Sinemet CR®). This perhaps explains the failure of Sinemet CR to reduce the risk

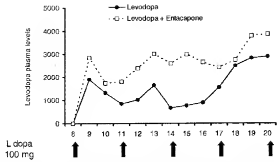

FIG. 2. Comparison of levodopa pharmacokinetics when administered at 3 hour intervals alone or in combination with a COMT inhibitor. Note that administering levodopa with the COMT inhibitor entecapone replicates the PK pattern seen with a levodopa infusion (see Fig. 1).

of motor complications in comparison to standard levodopa in the Sinemet CR First study.[74]

In contrast, the pattern could be replicated by administering levodopa in conjunction with a catechol-*O*-methyltransferase (COMT) inhibitor. In the presence of a decarboxylase inhibitor, levodopa is primarily metabolized by COMT. Administration of levodopa with a COMT inhibitor increases its plasma half life from about 90 min to ~3 hours.[75] COMT inhibitors have primarily been used as adjuncts to levodopa in the treatment of PD patients with motor fluctuations.[76,77] We have speculated that if levodopa could be administered in combination with a COMT inhibitor at sufficiently frequent intervals, this might provide continuous dopaminergic availability to the brain and reduce the risk of motor complications.[78] Indeed, we found that administering levodopa/carbidopa (100/25) ± entacapone (200 mg) at 3-hour intervals avoids the low plasma trough levels seen with intermittent doses of regular levodopa, and provides a plasma PK pattern resembling that seen with a levodopa infusion (Fig. 2).[14] To test the effect of this approach on the risk of developing dyskinesia, we compared levodopa administered four times daily with and without entacapone in MPTP monkeys.[79] Animals receiving levodopa with entacapone had significantly fewer dyskinesias than did animals treated with levodopa alone. In addition, they experienced greater improvement in motor control and had less disability. We interpreted these results to support the concept that more continuous delivery of levodopa reduces the risk of developing dyskinesia. Interestingly, this benefit was not seen when MPTP monkeys were treated with levodopa plus entacapone administered at 5-hour intervals which does not avoid pulsatile stimulation.[80]

To test this concept in PD patients, a prospective, multicenter, double-blind, placebo-controlled study is now being conducted to compare initial levodopa therapy administered with and without entacapone (the STRIDE-PD study). All patients have been entered into the study, and results should be available in early 2009. If this approach proves to reduce the risk of motor complications, it would require that early PD patients receive levodopa + entacapone at 3-hour intervals from the start of therapy. While the inconvenience of taking a pill five times per day seems a worthwhile price to pay for not having motor complications (assuming the results are confirmed in the double blind trial), many clinical and pharmaceutical research groups are actively seeking a new levodopa formulation or a levodopa prodrug that can provide similar levodopa PK to an infusion, but that can be administered once or twice daily. One approach utilizes ethyl ester forms of levodopa linked to 2-phenyl-3-carboxymethyl-imidazopyridine compounds giving rise to the so-called Dopimid compounds.[81] Maleic and fumaric diamides of levodopa methylester have also been developed in liposomes as prodrugs, and have demonstrated to provide more continuous dopamine availability in the rat striatum.[82] Glycosyl derivatives of levodopa and dopamine have also been generated to try and enhance levodopa availability and permit dopamine to cross the blood brain barrier.[83] Numerous other biochemical and synthetic approaches have been attempted in an effort to develop a long-acting formulation of levodopa (or dopamine) that crosses the Blood brain barrier.[84–86] To date none of these prodrugs have been tested in PD patients.

While the development of a stable, long-acting prodrug or formulation of levodopa has to date proven to be a daunting challenge, such a preparation has the potential to provide all of the benefits of standard levodopa without motor complications, and would obviate the need for most of the other medical and surgical therapies that are currently used to treat PD today.

LIMITATIONS OF CONTINUOUS DELIVERY OF A DOPAMINERGIC MEDICATION

When treating with continuous administration of a dopaminergic therapy, the potential for receptor desensitization and tolerance must be considered. In animal models, continuous D1 receptor activation is prone to induce tolerance.[87,88] This is a particular concern with continuous delivery of dopaminergic agents which activate the D1 receptor. Indeed, 24-hour around-the-clock infusion is associated with intermittent periods of reduced antiparkinsonian benefits despite continued infusion.[89] Further, chronic 24-hour infusion has also

been reported to cause nocturnal psychosis in some patients.[90] These problems can generally be avoided by limiting infusions to the waking day.[39] In this situation, stopping the drug overnight appears to be sufficient to resensitize receptors, and benefits are immediately obtained on reinstituting therapy. Stopping the infusion in advanced PD patients, however, can lead to transient periods of dystonia (about 30 min) and worsening of parkinsonism, but in general most patients consider this to be a reasonable price to pay for the daytime benefits provided by continuous infusion. These issues are less likely to be problems for patients with early PD, but further studies are required.

LIMITATIONS OF LEVODOPA THERAPY

Levodopa treatment without motor complications would be a major benefit for PD patients. However, even with this scenario there are still several limitations to levodopa therapy. First, the issue of the potential toxicity of levodopa has not been fully resolved. Levodopa metabolism can lead to the formation of potentially toxic reactive oxygen species.[91] Clinically, there is no evidence that levodopa adversely effects disease progression,[2] but imaging studies demonstrate a reduction in biomarkers of nigrostriatal function in comparison to both dopamine agonists and placebo, consistent with the possibility that the drug has toxic effects.[2,92,93] This requires further clarification. Second, long-term studies suggest that features that do not respond to levodopa, such as freezing, falling, and dementia, are the major source of disability for advanced PD patients, and not motor complications.[94] These nonresponsive features probably reflect the widespread degeneration that occurs throughout the brain, spinal cord, and peripheral autonomic nervous system in PD, and there is no reason to think that the opportunity to introduce levodopa treatment in a more physiologic manner will influence their development. It is thus likely that even a future form of levodopa that prevents motor complications would still be associated with disability, and there will remain a need for the development of nondopaminergic and neuroprotective therapies for PD.

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EXHIBIT D

Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications

C Warren Olanow, Jose A Obeso, Fabrizio Stocchi

Levodopa-induced motor complications are a common source of disability for patients with Parkinson's disease. Evidence suggests that motor complications are associated with non-physiological, pulsatile stimulation of dopamine receptors. In healthy brains, dopamine neurons fire continuously, striatal dopamine concentrations are relatively constant, and there is continuous activation of dopamine receptors. In the dopamine-depleted state, standard levodopa therapy does not normalise the basal ganglia. Rather, levodopa or other short-acting dopaminergic drugs induce molecular changes and altered neuronal firing patterns in basal ganglia neurons leading to motor complications. The concept of continuous dopaminergic stimulation proposes that continuous delivery of a dopaminergic drug will prevent pulsatile stimulation and avoid motor complications. In monkeys treated with MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and patients with Parkinson's disease, long-acting or continuous infusion of a dopaminergic drug reduces the risk of motor complications. The current challenge is to develop a long-acting oral formulation of levodopa that provides clinical benefits but avoids motor complications.

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Introduction

Since its introduction in the late 1960s, levodopa has been the most widely used and most effective drug for the symptomatic therapy of Parkinson's disease. However, chronic levodopa therapy is complicated by the development of motor complications, which can be disabling, difficult to treat, and limit the usefulness of the drug.[1,2] The development of surgical therapies, such as pallidotomy and deep brain stimulation of the subthalamic nucleus and the internal segment of the globus pallidus (GPi), can provide effective treatment for levodopa-induced motor complications, but surgery has risks, is expensive, and does not provide antiparkinsonian benefits beyond what can be attained with levodopa. Medical therapy that provides the benefits of levodopa without motor complications would be a major advance in the treatment of Parkinson's disease.

During the past two decades, substantial evidence has accumulated indicating that levodopa-related motor complications in Parkinson's disease are associated with non-physiological, discontinuous, or pulsatile stimulation of striatal dopamine receptors, and can be prevented or reversed by long-acting dopaminergic drugs that theoretically provide more continuous stimulation of striatal dopamine receptors.[2] Central to this concept are observations indicating that dopamine neurons in the substantia nigra pars compacta (SNc) fire tonically at a nearly constant rate,[3,4] that striatal dopamine is maintained at a fairly constant concentration,[5,6] and that there is continuous activation of striatal dopamine receptors. Experience with continuous infusions of levodopa and dopamine agonists has shown the potential advantages of continuous delivery of dopaminergic drugs and inspired the therapeutic concept of continuous dopaminergic stimulation.[7,8] In this review, we describe the advances in our understanding of the organisation of the basal ganglia, the molecular and physiological changes that underlie motor complications, and the experimental and clinical data supporting treatment strategies based on continuous dopaminergic stimulation in Parkinson's disease.

Motor complications of dopaminergic therapy

In the early stages of levodopa treatment, patients with Parkinson's disease typically experience excellent benefits that are sustained even if an individual dose is missed. However, with chronic treatment, the duration of benefit after a given dose of levodopa becomes progressively shorter and begins to mirror the plasma half-life of levodopa.[9] Patients begin to experience fluctuations in motor function alternating between on responses with a good antiparkinsonian effect and off responses when levodopa does not adequately treat parkinsonian features. Fluctuations can also occur in non-motor features of the disease (eg, pain, anxiety, depression). In the most severe cases, patients can experience rapid oscillations between on and off states without an apparent association with the levodopa dose.[10]

Levodopa-treated patients can also experience involuntary movements or dyskinesias.[11] Dyskinesias typically occur in association with high concentrations of levodopa in the plasma and maximum improvement in the motor response (peak-dose dyskinesia). These dyskinesias are usually choreiform in nature, although they can also manifest as dystonia and other movement disorders. Less commonly, dyskinesias can appear at or just before the onset of the on response, disappear during the on period, and re-emerge as the off period begins (diphasic dyskinesias). Diphasic dyskinesias are typically comprised of large amplitude stereotypic, rhythmic, and repetitive movements of the legs that can be associated with parkinsonian features in other body regions. Patients with Parkinson's disease can also have off-period dystonia mostly localised to their legs and commonly accompanied by pain and a sustained abnormal posture.

In extreme cases, patients treated with levodopa can cycle between on periods, which are complicated by disabling dyskinesias, and off periods in which

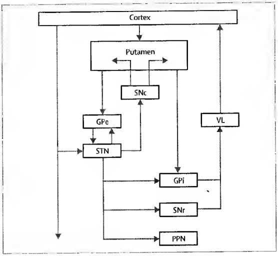

Figure 1: **Classic pathways of the basal ganglia**
GPe=globus pallidus; STN=subthalamic nucleus; SNr=substantia nigra pars reticulata; PPN=pedunculopontine nucleus; VL=ventrolateral nucelus of the thalamus. This classic model of the basal ganglia shows the direct and indirect striatopallidal pathways and that SNc neurons provide dopaminergic input to the striatum. The red arrows represent the excitatory pathways and the blue arrows the inhibitory pathways.

parkinsonism is uncontrolled and the patient is akinetic and frozen. With disease progression, delivery of a dose of levodopa that provides both a satisfactory antiparkinsonian effect and avoids dyskinesia becomes increasingly difficult.

Motor complications occur in about 50% of patients with Parkinson's disease who have received levodopa for more than 5 years, and in as many as 100% of patients with young-onset disease.[11,12] High doses of standard levodopa formulations are associated with an increased risk of motor complications in both animal models with MPTP lesions and patients with Parkinson's disease.[13,14] The recent ELLDOPA study showed that motor complications in levodopa-treated patients are dose-related and begin earlier than was previously appreciated.[15] After just 9 months of levodopa treatment (200 mg three times daily), 20% of patients experienced wearing off and 16% had dyskinesias.

Dopaminergic organisation of the basal ganglia

The classic model of the basal ganglia emphasises the direct and indirect striatopallidal pathways and the selective innervation of the striatum by dopaminergic neurons originating in the SNc (figure 1).[16,17] However, it is now appreciated that the basal ganglia function as a complex, integrated network with multiple feedback and feedforward loops rather than as the linear firing-rate-dependent system depicted in the classic model (figure 2).[18] Furthermore, dopaminergic innervation from the SNc is not restricted to the striatum but extends to include the subthalamic nucleus, internal and external segments of the globus pallidus, thalamus, and cerebral cortex.[19]

In healthy brain

Dopamine neurons fire tonically at a rate of 3–6 Hz independent of movement,[3,4] and striatal dopamine is maintained at a nearly constant concentration, as shown by both microdialysis and amperometry.[5,6] Phasic or burst firing of SNc neurons with release of larger amounts of dopamine can occur in association with reward or exposure to new stimuli.[20,21] However, the robust reuptake capacity of the dopamine transporter maintains constant striatal dopamine concentrations independent of the SNc neuronal firing rate.[5,6,22] Furthermore, axons of dopamine neurons that are activated by rapid firing branch profusely within the striatum[23] and interact primarily with dopamine receptors located within or next to the synapse where dopamine-transporter density is maximum.[24] These factors combine to maintain constant synaptic and extrasynaptic dopamine concentrations, thus permitting striatal dopamine receptors to be continuously exposed to dopamine. The constant firing rate of SNc dopamine neurons, stable striatal dopamine concentration, and the continuous activation of striatal dopamine receptors are essential for normal basal-ganglia function.[25]

SNc neurons also possess autoregulatory mechanisms, such as non-renewal, that help maintain stable neuronal firing rates.[26] Non-renewal firing implies that neuronal excitability is influenced by previous firing activity (for up to a few seconds), so that abrupt changes in discharge rates are modulated and overall firing activity remains fairly constant. Non-renewal in SNc neurons is probably mediated by intracellular mechanisms, such as after hyperpolarisation (calcium-dependent potassium current), local inhibitory effects of dopamine release, and feedback circuits such as striatonigral inhibitory projections.[27] These factors influence the probability of spike generation and regulate interspike variability.

A primary role of dopamine is to exert presynaptic modulation (in both up and down directions) on the glutamate-mediated excitation of striatal medium spiny neurons.[28–35] Most striatal neurons are medium spiny GABAergic neurons that receive massive glutamatergic inputs (ie, substantially more than 1000 per neuron) from terminals that originate in the cortex and thalamus and form asymmetric contacts with the heads of dendritic spines.[36,37] A smaller proportion of striatal inputs come from dopaminergic, cholinergic, and GABAergic neurons and form symmetric synaptic contacts. Striatal neurons primarily project to the globus pallidus (both external and internal portions) and make between 10 000 and 30 000 synaptic contacts per neuron.[17] Such an arrangement requires a precise selection mechanism to filter incoming and outgoing signals associated with movement, a function mediated in part by the effects of dopamine on both presynaptic and postsynaptic mechanisms. A study in mouse brain slices showed that dopamine can both enhance or suppress specific subsets of corticostriatal afferents by

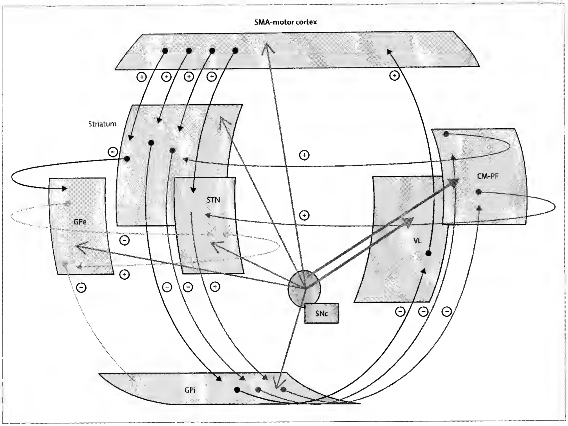

Figure 2: Modern paradigm of the basal ganglia pathways
SMA=supplementary motor area; GPe=globus pallidus; CM-PF=centromedian parafascicular nucleus; STN=subthalamic nucleus. This paradigm emphasises that the basal ganglia is a complex network manner with multiple feedback and feedforward loops. Note that SNc dopamine neurons provide dopaminergic innervation to multiple components of the basal ganglia in addition to the striatum. Reproduced with permission from Elsevier.[25]

activation of D2 receptors located presynaptically in glutamatergic terminals.[10] In this study, dopamine was shown to inhibit glutamate release from less actively firing corticostriatal afferents and to potentiate release from more active neurons. In functional terms, when a series of different cortical afferent signals converge on to a striatal medium spiny neuron, dopamine selectively enhances activity in the most powerful volley and inhibits others. We envision this mechanism allows a desired movement or action to be facilitated, while minimising the possibility of interference from conflicting neuronal activity.

Dopamine also acts postsynaptically to stabilise the firing rate and excitability of striatal neurons. Dopamine inhibits (via D2 receptors) or facilitates (via D1 receptors) striatopallidal neuronal activity.[18] Medium spiny striatal neurons usually express either D1 or D2 receptors, which give rise to projections forming the direct and indirect striatopallidal pathways, respectively (figures 1 and 2), although there is considerable crosstalk between these systems and they are probably not totally discrete.[19,40] Movement facilitation is associated with increased activity in the direct pathway and reduced activity in the indirect pathway.[16–18] Dopamine facilitates activity in D1-bearing neurons, which have an inhibitory effect on the pallidum, and inhibits activity in D2-bearing neurons, which lead to excitation of the pallidum.[31] Phasic firing induces the release of dopamine, which primarily activates D1 and D2 receptors within the synapse, whereas dopamine release associated with tonic firing primarily excites extrasynaptically located D1 receptors by volume transmission.[41] Under physiological conditions, tonic SNc firing predominates so that dopamine primarily activates extrasynaptic D1 receptors on neurons in the direct pathway that facilitate movement. Dopamine also modulates glutamate-mediated long-term potentiation and long-term depression and thereby regulates plasticity in striatal neurons.[42] Furthermore, dopamine exerts tonic inhibitory effects on cholinergic interneurons, which otherwise tend to increase the excitability of medium spiny striatal neurons by raising the amplitude of postsynaptic excitatory potentials evoked by cortical stimulation.[43,44]

Parkinsonian state

The studies described above illustrate that dopamine plays a major part in maintaining the stability of the basal ganglia network and is essential for the selection and processing of neuronal activity associated with normal movement. The situation changes in the dopamine-denervated state. The loss of dopamine nigral neurons impairs dopaminergic modulation of corticostriatal activity[45] and the capacity to develop long-term potentiation and long-term depression.[45–47] Although surviving dopamine cells in the SNc show little change in firing rate, autoregulatory mechanisms are impaired and there is a loss of the firing rate stability provided by non-renewal mechanisms.[48] As a result, there is a reduced capacity to compensate for small fluctuations in firing rate that promote instability of the basal-ganglia network. Dendritic spines on striatal medium spiny neurons, which are the sites of glutamate–dopamine interactions, are profoundly reduced in size and density.[49,50] Dual photon imaging shows that these changes are triggered by dysregulation of L-type calcium channels and selectively affect striatopallidal but not striatonigral neurons.[51]

The striatal dopamine deficit may initially be compensated for by downregulation of the dopamine transporter, heightened postsynaptic receptor sensitivity, and changes in subthalamic nucleus and GPi firing. These compensations might explain the interval between disease and symptom onset.[52,53] However, compensatory mechanisms eventually fail: D2-bearing medium spiny neurons (which coexpress enkephalin) become overactive whereas D1-bearing medium spiny neurons (which coexpress substance P and dynorphin) become hypoactive. This failure results in hyperactivity of neuronal activity in subthalamic nucleus and GPi neurons, excessive inhibition of thalamocortical and brainstem motor neurons, and the development of parkinsonian features.[16,17] In association with these changes, there is a reduction in the inhibitory centre surround—inhibition of neuronal firing in an area surrounding a firing neuron—that occurs in response to peripheral stimuli and abnormal synchronisation of neuronal firing in the striatum, subthalamic nucleus, and GPi of MPTP-lesioned monkeys and patients with Parkinson's disease.[54–60] The discharge rate of individual neurons in the globus pallidus is irregular and independent of firing in other nerve cells in normal monkeys, whereas in parkinsonian monkeys the discharge is oscillatory in individual neurons and synchronised between pairs of neurons.[61] These changes result in a loss of somatotopic selectivity and fundamentally impair the capacity of the basal ganglia to appropriately select and facilitate normal motor movement.

Levodopa-treated state

Dopamine replacement with standard doses of regular levodopa does not make the basal ganglia physiologically normal. Exogenous administration of repeated doses of short-acting levodopa (half-life of about 60–90 min) leads to large and uncontrolled oscillations in striatal and synaptic dopamine concentrations,[5,62,63] probably due to the loss of dopamine terminals and their capacity to buffer fluctuations in striatal dopamine concentrations. This leads to a change from the normal situation in which dopamine receptors are continuously exposed to dopamine, to one in which they are exposed to abnormally high or abnormally low concentrations of the neurotransmitter. This pulsatile stimulation destabilises an already unstable basal ganglia.

Acute administration of dopaminergic drugs like apomorphine or levodopa can reverse the firing-rate changes that accompany dopamine denervation in patients with Parkinson's disease and MPTP monkeys.[64–67] However, dopaminergic replacement with short-acting drugs does not restore basal ganglia neuronal firing patterns to normal. Heimer and colleagues[68] showed that although levodopa therapy influences GPi and GPe firing rates in MPTP-lesioned monkeys, they move in opposite directions such that the GPe to GPi firing-rate ratio is substantially increased in comparison to normal.[68] Furthermore, although levodopa reduces the percentage of correlated pairs of neurons with synchronous firing in the GPi and GPe of MPTP monkeys, they are not reduced to normal concentrations in the on state, and remain grossly abnormal during the off state. Levodopa use is also associated with specific changes in the expression and distribution of NMDA-receptor subunits. Gardoni and colleagues[69] showed that levodopa-induced dyskinesia is associated with profound changes in the distribution of NR2B subunits (from a synaptic to an extrasynaptic location) and in their association with members of the membrane-associated guanylate kinase (MAGUK) family of proteins. These and many other studies showed that standard levodopa therapy does not normalise the parkinsonian basal ganglia but shifts it to a different state of abnormality.

Discontinuous or pulsatile stimulation of striatal dopamine receptors

In Parkinson's disease, the progressive loss of SNc dopaminergic neurons causes striatal dopamine concentrations to be increasingly dependent on the peripheral availability of levodopa and impairs the capacity of dopamine terminals to buffer fluctuations in plasma levodopa concentrations. Thus variability in plasma levodopa concentrations associated with drugs having a short half-life results in variability in striatal dopamine concentrations and pulsatile stimulation of striatal dopamine receptors.

The effect of half-life in the production of dyskinesia can be readily observed in MPTP-lesioned monkeys. Short-acting dopaminergic drugs such as levodopa rapidly induce severe dyskinesias, whereas longer-acting dopaminergic drugs (eg, ropinorole, bromocriptine,

cabergoline) matched to provide comparable motor benefit are associated with little or no dyskinesias.[70–73] Indeed, intermittent injections of a short-acting dopamine agonist such as U-91356A or apomorphine rapidly induce dyskinesia, whereas continuous infusion of the same drug does not.[74,75] These experiments show that the same dopaminergic drug may or may not induce dyskinesia depending on whether it is given in a pulsatile or continuous manner.

Disease severity can also influence the risk that a drug will induce pulsatile stimulation and motor complications. MPTP-lesioned monkeys—with about a 95% loss of dopamine neurons—develop dyskinesias within days of starting levodopa treatment,[70,71] whereas partially lesioned or normal animals are much more resistant to the development of levodopa-induced dyskinesias.[74,76] Similarly, patients with Parkinson's disease are estimated to have a 40–60% loss of SNc dopamine neurons at the time of diagnosis and typically do not develop severe dyskinesias for years after starting levodopa. By contrast, patients with MPTP toxicity or parkin mutations who have severe dopaminergic lesions can develop severe dyskinesias within weeks of starting levodopa.[77,78]

Pulsatile stimulation of striatal dopamine receptors can induce molecular and neurophysiological changes in striatal neurons that are associated with dyskinesias. Studies in dopamine-denervated mice, rats, and monkeys showed that dyskinesia induced by short-acting dopaminergic drugs is associated with altered expression of various genes or proteins including preproenkephalin, preprodynorphin, cFos, delta FosB, JunB, Cdk5 (cyclin-dependent protein kinase 5), ERK1/2 DARP32, and D1-signalling proteins.[79–84] Similar findings have been reported in post-mortem brains of patients with Parkinson's disease; preproenkephalin expression was substantially higher in patients who had levodopa-induced dyskinesia than in patients treated with levodopa who did not have dyskinesia or normal controls.[85] Neither the gene changes nor the dyskinesia associated with a short-acting dopaminergic drug are reported when the same drug is given by continuous infusion.[79] The neurophysiological firing pattern of basal-ganglia neurons is also influenced by pulsatile dosing with a dopaminergic drug. Changes in the number and duration of pauses and bursts as well as in firing frequency have been reported in both MPTP-lesioned monkeys and patients with Parkinson's disease.[86,87] Furthermore, pulsatile administration of levodopa substantially changes GPe to GPi firing-rate ratios,[68] does not fully eliminate synchronous firing,[68] and impairs mechanisms involved in long-term depression and striatal plasticity.[47] How precisely these molecular and physiological changes lead to dyskinesia is not clearly understood.

Similar evidence supports the idea that motor fluctuations (ie, wearing off) are associated with pulsatile stimulation. In 6-hydroxydopamine-lesioned rats, chronic treatment with intermittent doses of levodopa is associated with a progressive reduction in the duration of the motor response following a single levodopa dose, but there is no shortening in the duration of the motor response after a dose of levodopa in animals that had previously been treated with continuous levodopa infusion.[88,89] As with dyskinesia, levodopa treatment regimens that induced shortening of the duration of the motor response were associated with altered expression of striatal preprodynorphin and prometenkephalin, whereas these gene changes did not occur with continuous levodopa administration.[90]

These findings show the inability of standard doses of oral levodopa therapy to restore basal-ganglia physiological activity to normal. They further demonstrate that non-physiological discontinuous or pulsatile dopamine replacement induces further disruptions in the dopamine-denervated basal ganglia leading to the development of motor fluctuations and dyskinesia.

Continuous-dopaminergic-stimulation-based therapy for Parkinson's disease

These laboratory observations have been extended to the clinic. In patients with early Parkinson's disease, several prospective double-blind, controlled trials have shown that patients randomised to initiate therapy with a long-acting dopamine agonist have a low risk of motor complications in comparison with patients treated with standard, short-acting levodopa—even though patients in both groups could receive supplementation with open-label levodopa if deemed necessary.[91–94] Indeed, very few, if any, patients treated exclusively with a long-acting dopamine agonist experience any dyskinesia at all. In each of these studies, patients initially randomised to receive levodopa had improved motor responses at all time points compared with patients initially assigned to receive a dopamine agonist. This finding prompted some to question if the reduced dyskinesia in the agonist group is associated with a less effective dopaminergic regimen.[95] However, agonist-treated patients could receive levodopa supplementation, and the very low frequency of dyskinesia seen with long-term dopamine-agonist monotherapy and the low rate of motor complications when the same drug is delivered by infusion make this explanation unlikely.

In patients with advanced Parkinson's disease, continuous infusion of levodopa or a dopamine agonist (apomorphine, lisuride) has been shown to provide long-lasting and dramatic improvement in established motor complications.[96] A prospective, controlled study with 40 patients with advanced Parkinson's disease with severe levodopa-related motor complications showed the benefit of continuous infusion. Patients randomly assigned to switch to a continuous subcutaneous infusion of lisuride had significantly less off time and dyskinesias than those remaining on standard oral formulations of levodopa.[97] These benefits lasted throughout the 4 year duration of

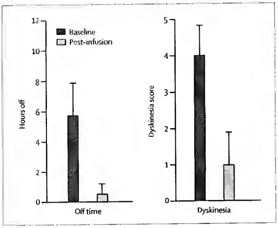

Figure 3: **Effect of continuous intraintestinal levodopa infusion on motor complications in Parkinson's disease**
Comparison of off time and dyskinesia scores at baseline when patients were on intermittent doses of standard levodopa, and at 6 months when patients were receiving levodopa by continuous intraintestinal infusion. Note that levodopa infusion was associated with a significant reduction in both off time and dyskinesia. Reproduced with permission from the American Medical Association.[109]

the study. Infusion was only given during the waking day to avoid tolerance. As a consequence, patients experienced some wearing off and dystonia when the infusion was discontinued at night, but both patient and physician global-rating scales indicated that infusion was associated with substantial and significant overall increases in quality of life. It should be noted that this was an open-label study, and double-blind trials of infusion therapies have not yet been done.

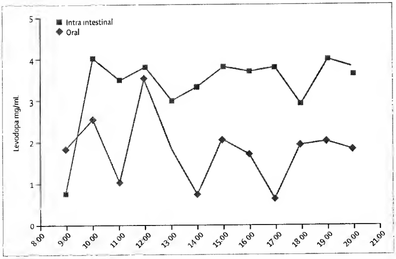

Figure 4: **Plasma levodopa concentrations after oral and continuous intraintestinal levodopa administration**
When levodopa was given orally patients experienced substantial motor complications but at 6 months, when levodopa was given by infusion, motor complications were much reduced. Note that infusion avoids the low trough concentrations seen with repeated oral doses of a standard levodopa formulation. Reproduced with permission from the American Medical Association.[109]

Implications for current treatment

On the basis of laboratory and clinical findings, many physicians now start treatment in appropriate patients with Parkinson's disease with a long-acting dopamine agonist and use levodopa when patients can no longer be satisfactorily controlled with dopamine agonist monotherapy.[98] This decision is partly based on the potential for short-term exposure to levodopa to prime for the development of dyskinesia. The concept of priming or sensitisation implies that patients exposed to levodopa for even a short time are more prone to develop dyskinesia when the drug is reintroduced than are patients who have never been exposed to levodopa.[81] This finding is thought to be associated with the capacity of levodopa to induce long-term plastic changes in striatal medium spiny neurons. Priming has been reported in MPTP-lesioned monkeys,[81] but remains a theoretical concept in patients with Parkinson's disease; this concept nonetheless represents another argument for begining therapy with a dopamine agonist. Dopamine agonists are not without complications (gastrointestinal problems, sleep disturbances with excess daytime sleepiness, peripheral oedema, psychosis, and possibly the induction of impulse disorders such as gambling) and are not typically used in elderly patients or in those with cognitive impairment. Although dopamine agonist monotherapy can be effective in early disease, patients eventually require supplementation with levodopa,[91,92] and levodopa can induce motor complications even if given in conjunction with a dopamine agonist.[73,91,92] Indeed, the time until the development of motor complications after the initiation of levodopa is about the same when levodopa is used as initial therapy as it is when levodopa is added to a dopamine agonist.[91] Thus dopamine agonists delay the introduction of levodopa but do not prevent or delay the development of motor complications once levodopa is initiated.

Current understanding of basal-ganglia physiology suggests that longer-acting or more continuous delivery of levodopa might avoid these motor complications. Controlled release formulations of levodopa did not reduce the risk of motor complications compared with standard levodopa in double-blind controlled trials,[99] but the controlled-release drug has variable absorption and was only given twice daily, so it is unlikely that continuous dopaminergic stimulation was achieved in this trial. Patch delivery provides a means of attaining stable plasma concentrations; however, this has proven difficult to achieve with levodopa because the drug is acidic and needs to be given with large volumes of fluid.[100] The only antiparkinsonian drugs currently being tested in a patch formulation are the monoamine oxidase-B inhibitor selegiline (primarily studied in depression) and the dopamine agonist rotigotine.[101] Neither of these drugs are effective enough to avoid the need for levodopa. Continuous infusion of a dopamine agonist has been shown to reduce motor complications in patients with

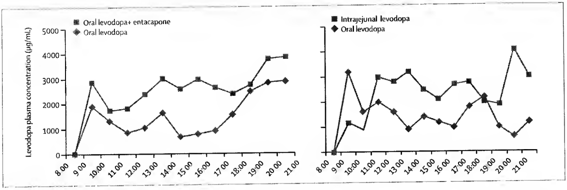

Figure 5: **Effect of intraintestinal infusion and addition of entacapone on levodopa pharmacokinetics**
Left: comparison of levodopa plasma pharmcokinetics profiles when levodopa and carbidopa were given at 3 h intervals with intermittent oral doses of a standard formulation and then 1 day later to the same patient at the same frequency, but in combination with the catechol-o-methyltransferase inhibitor entacapone. Note that oral levodopa is associated with low trough concentrations that are avoided when levodopa is combined with entacapone, thereby providing a pattern strikingly similar to that delivered continuously by infusion. Right: comparison of plasma pharmcokinetic profiles when levodopa is delivered orally with intermittent doses of a standard levodopa formulation and then again in the same patient when levodopa is given by continuous intraintestinal infusion. Note that oral levodopa in standard formulations is associated with low trough concentrations that are avoided when levodopa is delivered continuously by infusion or when it is combined with entacapone and given at 3 h intervals.[111] Reproduced with permission from Lippincott, Williams, and Wilkins.

advanced disease.[96] However, infusions are cumbersome are associated with side-effects at the site of administration, and patients with early disease will probably resist this treatment approach. Continuous levodopa delivery by intraintestinal infusion has been shown to reduce established dyskinesia in patients with advanced disease,[104–108] showing the value of continuous delivery of the drug. However, in addition to the problems associated with agonist infusions, continuous intraintestinal levodopa delivery requires a surgical procedure and frequent repositioning or replacement of the catheter.

An oral levodopa therapy that reflects the pharmacokinetics of a levodopa infusion would be a better alternative. To better understand the pharmacokinetic basis of motor complications, we compared the plasma levodopa pharmacokinetic profile in patients receiving oral doses of standard levodopa complicated by motor complications with that obtained in the same patients treated with a continuous levodopa infusion and who had experienced substantial improvement in off time and dyskinesias (figure 3).[109] These studies showed that levodopa infusion avoided the very low trough concentrations reported with intermittent doses of standard oral levodopa formulations (figure 4).[109] We speculated that in dopamine-lesioned patients with Parkinson's disease who cannot buffer fluctuations in plasma concentrations, low trough concentrations lead to low striatal dopamine concentrations and discontinuous or pulsatile stimulation of striatal dopamine receptors leading to the development of motor complications. We further speculated that the development of an oral levodopa treatment strategy, which mirrors the pharmokinetic profile obtained with a levodopa infusion, might similarly avoid motor complications. To try and accomplish this goal, we combined standard oral levodopa with a catechol-O-methyltransferase inhibitor, which blocks the peripheral metabolism of levodopa and extends its elimination half-life from about 90 min to about 3 h.[110] We found by giving levodopa and carbidopa in conjunction with entacapone at 3 h intervals we could avoid the low plasma levodopa trough concentrations observed with standard formulations of levodopa and carbidopa, and provide a plasma pharmacokinetic profile similar to that obtained from a continuous infusion (figure 5).[111] These findings suggest that levodopa, carbidopa, and entacapone given orally at 3 h intervals might provide more continuous dopamine stimulation than standard levodopa and reduce the risk of motor complications. Indeed, studies in MPTP-lesioned monkeys showed that levodopa-induced dyskinesias were significantly reduced when levodopa was given at approximate 3 h intervals in combination with entacapone.[112] The importance of avoiding pulsatile stimulation is shown by the fact that the addition of entacapone increases dyskinesia when levodopa is given at 6 h intervals and continuous dopaminergic stimulation is not achieved.[113] A prospective multicentre, double-blind study comparing the risk of motor complications in patients with Parkinson's disease randomly assigned to receive levodopa plus entacapone versus levodopa alone is currently underway (the STRIDE-PD study). Monoamine oxidase-B inhibitors, which block the central metabolism of dopamine, provide another theoretical opportunity to stabilise dopamine concentrations in the brain, although there is no experimental data for this approach.

Prospects for the future

The development of therapies based on continuous dopaminergic stimulation as a treatment for Parkinson's disease raises certain practical questions. Foremost,

will these therapies induce tolerance (or desensitisation) with degradation of the motor response? Studies in animals show that continuous 24 h administration of a dopaminergic drug can be associated with tolerance.[114] Similar results have been reported with 24 h infusions in patients.[115] Patients receiving round-the-clock 24 h infusions can also experience psychiatric problems with severe hallucinations.[96] These problems can generally be avoided with infusions that are given only during waking hours and we have not encountered tolerance or serious psychiatric problems with such infusion protocols.[97,109]

Finally, this review has focused on the scientific rationale and clinical results obtained with continuous dopaminergic stimulation as a treatment approach to Parkinson's disease. Other factors, such as the topography of the striatum, pattern of receptor denervation and activation, postsynaptic transcriptional alterations in medium spiny neurons, and abnormalities in glutamate and other neurotransmission systems may also play a part in the pathogenesis of motor complications. Indeed, other antidyskinesia treatment strategies may ultimately prove to be as or more effective than continuous-dopaminergic-stimulation-based strategies. Research has focused on the possibility that dyskinesia is associated with activation of specific dopamine receptor subtypes and dyskinesia has at times been linked to selective activation of either D1 or D2 receptors. However, dyskinesias can be induced with selective short-acting D1[116–118] or D2[119,120] agonists in MPTP-lesioned monkeys and patients. D3 receptors have also been implicated in the pathophysiology of dyskinesia in studies showing that a selective partial D3 agonist reduces dyskinesia and improves motor function in MPTP monkeys.[121] The levodopa molecule might also be particularly prone to induce dyskinesia. Indeed, Maratos and colleagues[122] reported less dyskinesia with short acting D1 and D2 agonists than with levodopa in MPTP-lesioned marmosets.[122] These findings do not, however, detract from the concept of continuous dopaminergic stimulation in the treatment of Parkinson's disease, because there are many studies in both animal models and patients in which dyskinesias associated with intermittent delivery of either levodopa or an agonist can be avoided with continuous delivery of the same drug.[74,75,109,119] Interestingly, parallel effects have been reported with respect to the ventral tegmental area and accumbens dopamine system and addiction where it has been found that intermittent discrete doses of psychostimulants result in rapid sensitisation, whereas continuous infusion of the same drug causes desensitisation.[123] We have also not considered the potential role of non-dopaminergic systems in the development of dyskinesia, and the possibility that other targets for antidysknesia therapies might include glutamate, cholinergic, adenosine2A and opioid receptors.[124] We have also not addressed diphasic dyskinesia, which may result from a different mechanism than peak-dose dyskinesia and may not be improved, or may even be worsened, by continuous delivery of suboptimal dopamine concentrations as we speculated have occurred in patients who underwent fetal nigral transplantation.[125] Nonetheless, a large body of scientific and clinical information supports the idea that discontinuous or pulsatile stimulation of striatal dopamine receptors contributes to the development of levodopa-induced motor complications and favours the use of continuous dopaminergic stimulation-based therapies in an attempt to obtain the symptomatic benefits of levodopa without motor complications. It is fascinating that 40 years after the introduction of levodopa, there is still a fundamental lack of knowledge on how to optimally give the drug.

Search strategy and selection criteria

References for this review were identified by searches of PubMed between 1980 and March 2006 using the search term "continuous dopaminergic stimulation".

Contributors

All authors contributed equally to the design, organisation, and writing of this review.

Conflicts of interest

CWO has consulted with Boehringer Ingleheim, Teva Neuroscience, Novartis/Orion Pharma, Schwarz, GSK, and Valeant. JAO has consulted with GSK, Boehringer Ingleheim, Teva/Lundbeck, and Novartis/Orion. FS has consulted with GSK, Boehringer Ingleheim, Teva Neuroscience, and Novartis/Orion.

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EXHIBIT E

Progress in Clinical Neurosciences: A Forum on the Early Management of Parkinson's Disease

Anthony E. Lang, Janis Miyasaki, C. Warren Olanow, A. Jon Stoessl, Oksana Suchowersky

ABSTRACT: There are numerous concerns related to treatment choices involving early dopaminergic therapy in Parkinson's disease. These include the effect on the underlying progression of the neurodegenerative process as well as the development of motor complications such as fluctuations and dyskinesias. A number of recent basic and clinical studies have provided new insights but have also added confusion and controversy. This report summarizes presentations and discussion dealing with these issues from a one-day symposium involving Canadian Movement Disorders neurologists.

RÉSUMÉ: Forum sur la prise en charge précoce de la maladie de Parkinson. Le traitement précoce de la maladie de Parkinson au moyen d'agents dopaminergiques soulève plusieurs questions, entre autres son effet sur la progression du processus neurodégénératif et sur le développement de complications motrices telles les fluctuations et les dyskinésies. Des études fondamentales et cliniques récentes ont fourni de nouvelles avenues de réflexion, mais elles ont également suscité la confusion et la controverse. Cet article résume les présentations et les discussions sur le sujet lors d'un symposium d'une journée tenue par des neurologues intéressés par les troubles du mouvement *(Canadian Movement Disorders Group).*

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Over the past five to ten years there have been important developments impacting on the initiation of dopaminergic therapy in early Parkinson's disease. Critical concerns relate to the potential neurotoxic effects of levodopa as well as the all too common development of motor complications. There have been significant advances in our understanding of the pathogenesis of motor complications, particularly levodopa-induced dyskinesias. A number of studies have evaluated clinical outcomes of initiating levodopa as well as comparative outcomes of early therapy with dopamine agonists versus levodopa. A variety of claims have been made with respect to the impact of these treatments on the underlying disease progression, particularly based on modern imaging techniques. There are a number of outstanding questions or sources of controversy in this literature. In order to review the "state-of-the-art" and address these critical issues a group of Canadian Movement Disorders experts met together for a one-day symposium in Toronto on May 8, 2004 funded by an unrestricted educational grant by Novartis, Canada. Four speakers were chosen to review the pertinent literature and to highlight and address the areas of uncertainty and sources of controversy. An open discussion with input from all participants followed each presentation and the discussion was recorded for subsequent review. The following reports summarize the presentations and discussion that took place at the meeting.

I. Pathogenesis of Motor Complications in Parkinson's Disease: New Approaches

CW Olanow

Levodopa therapy remains the "gold standard" for the symptomatic therapy of Parkinson's disease (PD). However, long-term treatment is associated with the development of potentially disabling motor complications[1]. This has limited the value of levodopa therapy and is largely responsible for the resurgence of surgical therapies in PD. Indeed, no medical or surgical treatment has been shown to provide superior efficacy to levodopa. There are non-dopaminergic features that limit the potential of levodopa therapy (e.g. dementia, autonomic disturbances, and postural instability). However, the ability to deliver levodopa so as to provide symptomatic benefits without

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complicating dyskinesia or motor fluctuations would represent a major advance in the treatment of PD.

Motor Complications

Increasing evidence indicates that levodopa-induced motor complications are related to abnormal pulsatile stimulation of striatal dopamine receptors.[2] Normally, dopamine neurons in the substantia nigra pars compacta (SNc) fire continuously, and the firing rate is not modified by the presence or absence of movement.[3] Thus striatal dopamine levels are stable and dopamine receptors are exposed to relatively constant levels of dopamine. Substantia nigra pars compacta dopamine neurons do burst in response to reward or increases in glutamate activation,[4] but terminal dopamine reuptake is sufficiently robust that synaptic dopamine levels remain constant.

In PD, because there is a loss of substantia nigra pars compacta dopamine neurons, striatal dopamine levels are dependent upon the peripheral availability of exogenously administered levodopa. There have been no studies that establish how levodopa should be administered in order to provide dopamine to the brain in a physiologic way. Indeed, the recently completed ELLDOPA study (as discussed by Dr. Suchowersky) is the first double blind, controlled dose ranging study of levodopa that has been performed to date.[5]

There is now considerable evidence indicating that pulsatile stimulation of dopamine receptors leads to gene and protein changes in striatal neurons with alterations in neuronal firing patterns and the consequent development of motor complications.[2,6] Two factors contribute to the likelihood that pulsatile stimulation will occur; disease severity and half life of the dopaminergic agent employed. With greater disease severity, there is greater degeneration of striatal dopamine terminals and a reduction in their capacity to buffer fluctuations in striatal dopamine levels. Indeed, levodopa-induced dyskinesia emerge within days in MPTP monkeys where there is a 95% loss of nigral neurons, whereas they develop over months or years in PD patients where there is typically a 30-60% loss of dopamine neurons at the time symptoms first appear. Studies in MPTP-lesioned monkeys also illustrate the importance of plasma half life in the induction of dyskinesia.[7,8] Short-acting dopaminergic agents such as levodopa provide benefit that is associated with dyskinesia. In contrast, long-acting dopamine agonists provide comparable benefit, but with a marked reduction in both the severity and frequency of dyskinesia. Indeed, dyskinesia are seen with pulsatile administration of a short-acting dopamine agonist, but not when the same agent is administered by continuous infusion.[9]

These studies suggest that therapies that provide more constant activation of dopamine receptors (Continuous Dopaminergic Stimulation) might be associated with reduced motor complications. Several prospective, randomized, double-blind, controlled studies have been performed in early untreated PD patients, comparing initial therapy with a short-acting formulation of levodopa and a long-acting dopamine agonist.[10,11] Each study showed reduced motor complications in patients started on therapy with the dopamine agonist, even when initial therapy was supplemented with open label levodopa (as discussed by Dr. Miyasaki).

These results support the early use of dopamine agonists in the treatment of early PD patients. However, patients randomized to levodopa in these studies have improved UPDRS motor scores compared to patients treated with dopamine agonists. Further, virtually all PD patients eventually require levodopa. The ropinirole study showed that patients receiving dopamine agonist monotherapy had hardly any motor complications, while supplemental levodopa increased the frequency of motor complications even in the presence of a dopamine agonist.[10] Indeed, the risk of developing dyskinesia is the same regardless of whether levodopa is introduced as initial therapy or as a supplement to the dopamine agonist (Personal communication – O Rascol).

It is thus evident that PD patients require levodopa, and that levodopa is associated with an increased risk of motor complications regardless of whether or not the patient is also taking a dopamine agonist. A key question is whether or not the risk of developing motor complications with levodopa could be reduced if the drug was administered in a longer-acting formulation. Continuous infusion of levodopa is known to be associated with reduced off time and reduced dyskinesia in comparison to the standard oral formulations of the drug.[12-19] We recently confirmed this observation and performed pharmacokinetic (PK) studies when the patients were receiving oral levodopa and experiencing severe motor complications and then when they were receiving levodopa by infusion with a marked reduction in motor complications.[20] The major distinction in these two PK patterns was that oral levodopa was associated with very low trough levels, while continuous infusion largely eliminated the low trough levels seen with oral delivery. These low trough levels likely represent periods during which striatal dopamine levels are reduced and striatal dopamine receptors are not activated, and thus may represent the pharmacologic basis of pulsatile stimulation. This PK pattern can serve as a template for designing an oral treatment strategy that models infusion. If an oral treatment strategy can be developed that mirrors the PK pattern of a continuous levodopa infusion, it is reasonable to consider that comparable clinical benefits with reduced motor complications might be obtained.

Frequent doses of regular formulations of levodopa (up to hourly) and controlled release formulations of levodopa do not prevent the development of low plasma levodopa trough levels (Stocchi and Olanow, unpublished data). We have, however, been able to avoid low trough levels and simulate the PK pattern of levodopa infusion by administering levodopa in combination with a catechol–O–methyltransferase (COMT) inhibitor.[21] Catechol–O–methyltransferase is the major metabolic pathway for levodopa in the presence of a decarboxylase inhibitor, converting approximately 90% of orally administered levodopa to the inactive product 3-O-methyldopa.[22] The addition of a COMT inhibitor increases the elimination half-life of levodopa, and thus reduces its potential to induce pulsatility. In MPTP-lesioned monkeys, administration of levodopa in combination with entacapone significantly reduces the risk of dyskinesia in comparison to when levodopa is administered alone.[23]

These studies collectively suggest that, in PD patients, it may be preferable to initiate levodopa therapy (given with an aromatic acid decarboxylase inhibitor) in combination with a COMT inhibitor in order to obtain maximal efficacy coupled

with reduced risk of motor complications. At this time there is no evidence from clinical trials that this combination will reduce the risk of motor complications. To test this hypothesis, we have organized a prospective, double blind, clinical trial (STRIDE-PD). In this study, PD patients who require levodopa/carbidopa will be randomized to receive the drug in combination with entacapone or placebo. Patients will be included who are, and who are not, on dopamine agonists. Positive results in this study will support the introduction of levodopa therapy in combination with a COMT inhibitor and will likely influence the way PD patients are managed in the future.

II. Levodopa therapy in early PD

O Suchowersky

Since its introduction in the 1960s, levodopa has been recognized to be the most effective treatment for Parkinson's disease.[24,25] All major motor symptoms show significant improvement, as do activities of daily living and quality of life, and it remains the most effective treatment over the course of the disease. Additionally, use of levodopa has been shown to increase life expectancy. Untreated PD patients have a life expectancy of under 10 years;[26 27] the advent of levodopa has reduced this mortality by half[28] and longevity was increased in those who began levodopa earlier, at a time of less disability, compared to those who were started very late in the disease process.[29]

Most patients require symptomatic therapy within 48 months of symptom onset.[30] The most common reasons given for therapy initiation include development of gait and balance problems, worsening of bradykinesia, and tremor so job security is threatened, or decline in ability to perform activities of daily living.[31]

Starting levodopa in de novo patients results in approximately a 30% improvement in the UPDRS.[11,32,33] Benefit is most significant in rigidity and bradykinesia. Patients typically can be managed on 300-600mg/ day in the first two to six years with little need for upward dose adjustment. With disease progression, the level of disability returns to the pretreatment baseline within five years. The benefit of levodopa in PD is usually so significant that lack of responsiveness has implications for diagnosis, i.e. the individual likely has another form of Parkinsonism.

A recurring question is whether initiation of levodopa should be delayed, and if early initiation promotes development of dyskinesias, motor fluctuations, and/or alters disease progression.[34,35] A number of retrospective studies have suggested that disease progression and development of motor fluctuations is dependent on disease duration, rather than duration or dose of levodopa exposure.[36-39] One study showed that the effect on prolongation of life expectancy is more pronounced with earlier initiation of levodopa.[28]

To answer this question, a prospective double-blind randomized controlled trial was recently organized by the Parkinson Study Group. The ELLDOPA study[5] enrolled 360 de novo patients and randomized them to three doses of levodopa/carbidopa (150/37.5mg, 300/75mg and 600/150mg) and placebo. Patients were evaluated over a 40-week period followed by a two-week washout. The study was the first double-blind controlled trial to demonstrate a dose-related improvement in the motor features of PD in response to levodopa. After the two-week washout, the levodopa treated patients, particularly in the 600 mg group, remained significantly better than those receiving placebo. This suggests that levodopa may have reduced disease progression, although, it is possible that the two-week wash out was simply not long enough to eliminate a very long pharmacological effect. A smaller subgroup of patients underwent, β–CIT SPECT scanning (see discussion of Dr. Stoessl). Here, in contrast to the clinical results, levodopa was associated with a greater decline in striatal dopamine transporter function than placebo. Once again, it is not possible to differentiate a negative effect on disease progression, which was certainly not supported by the clinical results, from a direct effect on the uptake of the ligand unrelated to changes in the disease process. Thus, current recommendations are that patients should be started on dopaminergic therapy such as levodopa when disease progression starts to result in disability, in order to experience maximum benefit.[40] Dyskinesias (typically very mild) developed in approximately 16% of patients in the high-dose group (600 mg/day) after only nine months of treatment. This emphasizes the need to pursue methods of delaying the motor complications of levodopa at the same time as trying to evaluate whether the results of the ELLDOPA trial favor early introduction of levodopa for disease modification.

With disease progression, effectiveness of levodopa diminishes. Initially, an overall loss of benefit is seen, followed by development of wearing off. The patient develops cramping in the legs during the night ("off" dystonia). Each dose of levodopa lasts for a shorter duration of time.[41]

Dyskinesias begin to occur. The prevalence and incidence of motor complications (dyskinesias, fluctuations) has been the subject of many studies. Somewhat different results have been obtained, due to differences in methodology, and definitions of motor complications. Overall, they have been reported to develop in 20-59% of patients at five years.[11,32,33,42]

Are some formulations of levodopa preferable to others with respect to improving symptomatic control and decreasing rate of complications? Two long-acting (continuous release) preparations are currently available, Sinemet CR®, and Madopar HBS®. It has been suggested that use of these preparations will result in continuous dopaminergic receptor stimulation and result in later development of motor complications, as compared to standard preparations.

The first multicentre study[43] compared Madopar HBS® to standard Madopar in 134 de novo patients over a five-year-period in a randomized double-blind parallel-group design. No significant differences were found in daily dose of levodopa, number of doses, or therapeutic benefit at five years between the two preparations. Using the UPDRS Part IV scale, almost 60% of patients experienced wearing off, up to 20% experienced early morning dystonia and 41% had dyskinesia within five years in each group.

The second study[32] compared Sinemet® vs. Sinemet CR®. This international randomized, double-blind study enrolled 618 patients. At the end of five years, the dose of levodopa and rate of fluctuations and dyskinesia showed no significant difference between the two groups. The rate of motor complications (fluctuations and dyskinesias) was 21-22%. Thus, long acting levodopa preparations did not show an advantage over standard levodopa in postponing or reducing motor fluctuations. The

lower incidence of motor complications in the second study likely reflects the differences in collecting the information. It should be emphasized that the infrequent dosing used in both studies would not have been expected to eliminate pulsatile stimulation of dopamine receptors which may be critical to the development of motor complications. Thus, study methodology may have largely precluded obtaining a positive result since dosing at a minimum of four to six times per day with a controlled-release preparation would have probably been required to truly provide a more continuous form of drug administration.

Another way of prolonging duration of action of levodopa is by adding a COMT inhibitor such as entacapone. Entacapone acts peripherally, decreasing degradation of levodopa, thus increasing availability centrally. The combination has been shown to be effective in increasing "on" time and decreasing "off" time in PD patients with advanced disease.[44] The question of whether the initiation of levodopa with COMT inhibition will result in a reduced incidence of motor complications has been addressed by Dr. Olanow in the previous section.

Does addition of entacapone to stable non-fluctuating patients on levodopa result in any benefit? The UK-Irish study[45] studied both fluctuating and non-fluctuating subjects over a six-month-period in a blinded fashion. One hundred and twenty eight non-fluctuating patients were enrolled, with the primary efficacy measure being part II of the UPDRS (activities of daily living). Activities of daily living (ADL) scores showed a small but significant improvement in the entacapone group (10.6 to 10.0 points) compared to a worsening in the placebo group (9.4 to 9.5 points) at a mean interval of four months. The total daily dose of levodopa increased by 40 mg in the placebo group with no significant increase in the entacapone group.

In the CELOMEN study,[46] PD patients, mostly with advanced disease, were studied for six months to determine safety and efficacy of entacapone as compared to placebo. Only 13% (41 out of 300) were non-fluctuating. In this small cohort, patients treated with entacapone showed a small improvement in both ADL and motor unified Parkinson's disease rating scale (UPDRS) (1 and 2.3 points respectively), while the placebo group showed a slight deterioration (1.5 and 2.1 points respectively). A decrease of 24mg of total daily dose of levodopa was seen in the entacapone group. Results did not reach statistical significance most likely due to small sample size.

In the US-01 study[47], 750 levodopa-treated, stable (non-fluctuating) patients were enrolled in a prospective, double-blind, multicentre 26-week study. Patients were randomized to receive either entacapone or placebo with each dose of levodopa. Levodopa dose increase was not permitted and the primary outcome measure was change in the UPDRS motor score from baseline. No significant change was seen in the primary outcome measure in the two groups. However, the entacapone group showed a statistically significant improvement in a variety of measures of quality of life including PDQ-39, and SF-36. Also, a larger number of placebo patients required levodopa rescue.

Thus, addition of entacapone to PD patients with early disease may result in improvement in quality of life and ADL, without improvement in motor function. However, caution in interpretation of these results should be used, as there were a large number of dropouts during the trial. The question remains whether use of COMT inhibition with levodopa in de novo patients results in delay in motor complications, and further studies to answer this important question are needed.

III. Dopamine Agonists in Early Parkinson's Disease

Janis Miyasaki

Morbidity and mortality in Parkinson's Disease are dramatically reduced with levodopa[48] (as discussed by Dr. Suchowersky). However, levodopa treatment is also associated with motor complications. Motor complications such as wearing off, on-off phenomena, sudden offs and freezing – and dyskinesias including painful dystonia affect approximately 70% of patients within five years of starting levodopa.[49] A study of the impact of dyskinesias over the first four years of dopaminergic therapy did not show a significant negative impact on quality of life by dyskinesias.[50] The impact of dyskinesias over the longer term is unclear.

Dyskinesias themselves can cause disability through interference with the performance of activities of daily living and indeed they are the major reason for consideration of surgical procedures for PD.[51] Therefore, attention has turned from symptom control alone to the need to provide satisfactory symptom control and avoid the onset of motor complications. Although the exact molecular basis for these motor complications is controversial, pulsatile stimulation of dopamine receptors by short-duration drugs such as levodopa is felt to be key[52,53] (as discussed by Dr. Olanow). Hence, even dopamine agonists can induce motor complications if their duration of action is short. Available dopamine agonists such as bromocriptine, pergolide, pramipexole and ropinirole have longer half-lives. Of note, the dopamine agonist with the longest half-life, cabergoline, is not available in Canada for the treatment of PD.

Beyond avoidance of motor complications, dopamine agonist therapy theoretically could be associated with a slower progression of illness than levodopa. This theory is partially based on the assumption that levodopa treatment accelerates the progression of PD[54]. In this paradigm, dopamine is metabolized to toxic-free radical species. Therefore, levodopa treatment further increases dopamine turnover and hence increases free radical formation thereby causing further nigral cell death.[55] Dopamine agonists permit the use of lower doses of levodopa, thus acting as sparing agents and theoretically reducing the free radical burden. Furthermore, dopamine agonists reduce dopamine formation and turnover through D2 autoreceptor stimulation and further reduce free radical formation. Dopamine agonists may also have direct antioxidant properties and effects on mitochondrial membranes.[56] Indeed, both pramipexole and ropinirole are proposed as potential neuroprotective drugs for further evaluation in Parkinson's disease by the National Institutes of Health.[57]

The reader is directed to an evidence-based practice parameter dealing with the initiation of treatment in early disease published by the American Academy of Neurology in 2001.[40] Since this was completed prior to the follow-up publication of the pramipexole study and recent reports describing problematic non-motor complications of Parkinson's disease, here we will concentrate on an update of the pivotal trials evaluating longer term treatment of Parkinson's disease with dopamine agonists

published in peer-reviewed journals and studies describing side effects of treatment.

Pramipexole

A four-year study compared pramipexole to levodopa/ carbidopa (CALM-PD).[58] Patients symptomatic for less than seven years were randomized to pramipexole or levodopa therapy. Assigned drug was escalated over ten weeks. After this time, further symptomatic benefit required the addition of open-label levodopa. For the final 1.5 years of the study, subjects could increase or decrease the dose of their study drug, or add sustained-release levodopa, amantadine or a COMT inhibitor in addition to open-label levodopa in an effort to replicate accepted practice. The primary outcome variable was the time to development of any motor complication (wearing off, dyskinesias, on-off fluctuations or freezing). The secondary outcome variables were changes in scores for the UPDRS, two quality of life scales (PDQUALIF and EuroQol Visual Analog Scale) and time to require open-label levodopa.

Three hundred and one patients participated in the study. Baseline characteristics were similar in the two groups. A significantly higher number of patients in the pramipexole group required open-label levodopa (72%) compared with 59% in the levodopa group. The primary outcomes were statistically different in favour of pramipexole with only 52% of the pramipexole group reaching endpoint compared with 74% of the levodopa group for dyskinesias and wearing off.

Secondary outcome variables showed improved UPDRS scores for levodopa compared with pramipexole in all domains (mental status, activities of daily living, motor scores). Quality of life variables did not reveal a difference between pramipexole and levodopa treated subjects.

A parallel study used single photon emission computed tomography (SPECT) brain imaging using the dopamine transporter molecule beta CIT.[59] Patients were scanned at baseline and at regular intervals (22, 34, 46 months of treatment). Patients randomized to levodopa had greater declines in ligand binding. This may indicate greater loss of striatal dopamine terminals or that initial therapy with dopamine agonists modulates the dopamine transporter rather than conferring neuroprotective benefit (these issues are discussed in greater detail by Dr. Stoessl). Further, UPDRS scores were similar in the levodopa and pramipexole group after 46 months, making neuroprotection unlikely.

Ropinirole

A five year study of ropinirole versus levodopa for early treatment of Parkinson's disease demonstrated significantly greater motor benefit in subjects randomized to levodopa.[10] There was no significant difference between the treatment groups at five years based on the activities of daily living portion of the UPDRS. The absolute risk reduction for dyskinesias after five years of treatment was 26% for the ropinirole group. If disabling dyskinesias were considered alone, the absolute risk reduction was 14% in the ropinirole group. The number needed to treat with ropinirole monotherapy was seven in order to avoid the development of dyskinesias.

Conclusions: Motor benefit and complications of treatment

Motor benefit therefore is superior for levodopa compared with dopamine agonists in monotherapy use. However, the risk of developing motor complications is far greater with levodopa. In the short term (four years), dyskinesias do not reduce quality of life. Although these studies examined an important clinical question, other questions arise from close examination. Perhaps the difference in rates of motor complications relates directly to the degree of motor benefit obtained. If dopamine agonist motor benefit was equivalent to levodopa, would motor complications still be reduced with dopamine agonist monotherapy? Further, what would different treatment strategies achieve? For instance, if patients received initial dopamine agonist therapy and then used levodopa "rescue" for further motor benefit, would this be superior to levodopa initiation followed by dopamine agonist "rescue"? That is, would either strategy be superior to monotherapy in providing optimal motor benefit and a reduced or acceptable risk of motor complications? Finally, what is the effect of dyskinesias on quality of life in the longer term? Will this new treatment paradigm reduce the number of patients requiring surgery for control of symptoms and dyskinesias?

Another issue to examine is the cost to the patient in terms of non-motor side effects.

Non-motor side effects of anti-parkinsonian treatment

Common side effects of antiparkinsonian treatment include nausea, vomiting and orthostatic hypotension. Based on the above studies pramipexole caused more somnolence, hallucinations and generalized and peripheral edema compared with levodopa. Ropinirole compared with levodopa induced more hallucinations (17% vs 6%), leg edema (14% vs 6%) and somnolence (27% vs 19%). However, ropinirole and levodopa had similar over all adverse event rates and equivalent drop out rates due to complications.

Subsequent to these studies, the risk of sudden onset of sleep became apparent. The initial report entitled "Falling Asleep at the Wheel" described eight patients treated with pramipexole and one patient, subsequently switched to ropinirole, experiencing sudden falling asleep while driving.[60] This report used the term "sleep attacks" since the patients reported no prior daytime somnolence and sudden, unavoidable onset of sleep while driving. Subsequent investigators argued that somnolence did not occur without warning but patients ignored cues of somnolence; therefore the term "attack" was inappropriate.[61] In addition, legal ramifications of automobile accidents gave patients incentive not to recall somnolence prior to the accident. One centre has gone so far as to state that daytime somnolence is an integral feature of Parkinson's disease.[62] Nonetheless, somnolence is still underrecognized in Parkinson's disease and can increase with antiparkinsonian treatment. Although most patients falling asleep do so with the usual warnings, rare patients have been documented to demonstrate more rapid transitions from wakefulness to deeper stages of sleep.[63] Levodopa is least likely to cause sudden onset of sleep while cabergoline, pramipexole and ropinirole uncommonly cause sudden onset of sleep.

Although newer dopamine agonists are not ergot based, they seem to cause leg swelling and edema in a significant portion of patients. Recent reports indicate cardiac valvular fibrosis occurs

with pergolide use[64,65]. In those taking pergolide, 5 mg/day or more, 33% had significant valvular fibrosis. In lower doses, 19% of patients had important restrictive valvular heart disease.[65] In the control group, no patients had valvular heart disease. Therefore, patients requiring higher doses of pergolide should be monitored for occurrence of cardiac valvulopathy. This may be at least partially reversible following pergolide withdrawal. There is no consensus on the best methods of screening for the presence of restrictive valvulopathy in at-risk patients or whether the benefit of maintaining therapy with pergolide or another ergot dopamine agonist justifies the risk in patients whose symptoms are currently well-controlled. A logical approach would be to have an open discussion with the patient explaining the nature of the problem and the current status of uncertainty. Patients should undergo screening echo-cardiography. Patients wishing to be taken off the ergot should be switched to alternative treatment independent of the presence of valvular changes. If abnormalities consistent with restrictive valvulopathy are found on echocardiography, patients should be withdrawn from the ergot agent and switched to a non-ergot agonist or another alternative therapy. This new concern needs to be factored when considering an ergot as the first-line dopamine agonist in the treatment of Parkinson's disease.

Conclusions: Non-motor side effects

Non-motor side effects of antiparkinsonian treatment are common and significant. The incidence of hallucinations, generalized and peripheral edema are greater for dopamine agonists than levodopa. Although somnolence can occur with all antiparkinsonian treatment or even prior to treatment, levodopa is the least likely to cause more problematic excessive daytime somnolence that occasionally manifests as "sudden onset of sleep" while driving. Cardiac valvulopathy and other fibrotic complications of ergot-derived dopamine agonists are an increasing concern.

Which drug to start with – Dopamine agonists or levodopa?

An economic study of pramipexole compared with levodopa demonstrated cost savings with pramipexole monotherapy.[66] The main benefits were avoidance of motor complications and reduced requirement for costly surgery. However, dyskinesias do not have impact in early stages of illness on quality of life. Their impact in later stages of illness remains unclear. Further, the costs of other non-motor side effects were likely underestimated since, with expanded dopamine agonist use, other side effects such as punding and gambling are increasingly reported.[67-71]

At this time, when initiating symptomatic treatment with either a dopamine agonist or levodopa, the physician needs to consider the risk of dyskinesias to the individual patient, their requirement for rapid symptom control and their ability to tolerate dopamine agonists. Therefore, patients at high risk of hallucinations (e.g. cognitive compromise) or daytime somnolence as predicted by the Epworth Sleepiness Scale and possibly obsessive-compulsive behaviour should probably be started on levodopa rather than a dopamine agonist. Although well-designed and executed trials examine discrete scientific questions and evidence-based reviews can synthesize the best available information for specific patient populations and situations, the decision for individual patients takes a myriad of uncontrolled patient characteristics into account and thus remains the privileged domain of the individual clinician and his or her patient.

IV. Functional Imaging Studies in Early Parkinson's Disease

J Stoessl

Functional imaging studies can potentially be of enormous use in studying the natural history and progression of Parkinson's disease. Other potential applications include assistance in early diagnosis (particularly if disease modifying therapies become available) and understanding the pathogenesis of longterm complications of therapy. However, the interpretation of these studies can be a minefield, and it is important for anyone reviewing the results to understand the potential pitfalls.

Several approaches are available to assess the integrity of the nigrostriatal dopamine system. The majority of these measure some function that is relatively specific to dopamine neurons. Thus, 6-[^{18}F]fluoro-L-dopa (6FD) is taken up by monoaminergic neurons, decarboxylated to 6-[^{18}F]fluoro-L-dopamine (6FDA) and 6FDA activity is trapped in synaptic vesicles. If decarboxylation activity is subnormal, or there is reduced capacity to trap 6FDA, the uptake (usually measured as a graphically determined uptake constant, Ki or Kocc) will be reduced. This has traditionally been regarded as the gold standard for assessing the integrity of the dopamine (DA) system, particularly as 6FD uptake has been shown to correlate with nigral DA cell counts in humans[72] and in monkeys with MPTP-induced parkinsonism.[73] The membrane dopamine transporter can be labeled with a number of positron-emitting ([^{11}C] or [^{18}F]-labeled) compounds, or with γ-emitters for single photon emission computed tomography (SPECT). The majority of these compounds are tropanes (cocaine derivatives), although another option is the positron emitting [^{11}C]*d-threo*-methylphenidate.[74] Finally, the vesicular monoamine transporter type 2 (VMAT2) can be labeled using [^{11}C]dihydrotetrabenazine (DTBZ).[75] Imaging studies with any of these tracers show marked (approximately 40%) reductions in early PD, with a characteristic pattern in which the posterior striatum is affected more than the anterior striatum, in an asymmetric fashion (as is characteristic of the clinical features). Although it was initially hoped that this pattern might help differentiate idiopathic PD from other "Parkinson-plus" syndromes,[76] it has become apparent over time that this differentiation is not reliable, and the rostro-caudal gradient seen in Parkinson's Disease may also be seen in multiple system atrophy,[77] and in parkinsonism associated with viral encephalitis[78] and spinocerebellar atrophy type 2.[79] It should be noted that in the latter disorder, raclopride binding to dopamine D2 receptors may be increased with a rostrocaudal gradient complementary to the reduction of 6FD uptake, in contrast to multiple system atrophy. 6FD uptake can be used to detect preclinical abnormalities in subjects exposed to MPTP[80] or in asymptomatic individuals with a genetically determined risk of PD who ultimately go on to develop clinical manifestations.[81] All of these tracers show abnormalities in the clinically unaffected striatum in patients with clinically unilateral PD.[82-85]

Another approach to functional imaging is the study of changes in regional cerebral glucose metabolism. Although

traditional comparisons of specific regions may be relatively unrewarding in PD, the application of Principal Components Analysis to the data may reveal altered patterns of connectivity that can be quite specific to PD (or at least levodopa-responsive parkinsonism) and not seen in other disorders that result in parkinsonism.[86].

Attention has been focused on the merits and pitfalls of functional imaging studies in PD in the last couple of years because of studies in which the imaging outcome measures suggested that certain treatments might modify disease progression, while the clinical data either failed to support this, or indeed suggested changes in the opposite direction. The potential usefulness of a biomarker of disease progression is clear: clinical measures of PD progression are subject to many problems in interpretation. These include confounds related to unanticipated symptomatic effects of the intervention (as demonstrated so well by the DATATOP study[87-89]), difficulties achieving full washout of the intervention (as seen in DATATOP and, as well, possibly in the recent ELLDOPA study[5]) and the often poor correlation between nigral cell counts and clinical function. Clinical measures are subject to considerable variance, and this may result in the need to study large numbers of subjects in order to detect a statistically significant effect of the intervention, particularly as there may be a large placebo effect in PD.[90]

In the CALM-PD study (as discussed by Dr. Miyasaki), a subgroup of patients who were randomized to receive initial treatment with either levodopa or pramipexole had SPECT scans with the DAT marker [^{123}I]β-CIT. The rate of decline in [^{123}I]β-CIT uptake was greater in patients treated with levodopa than in those treated with pramipexole. However, clinical measures of parkinsonism (assessed 12 hours off medication) favoured levodopa at two years, and were not different between groups at later time points.[59] Apart from this striking paradox, there were other difficulties with the interpretation of the results. First, the major difference between the groups seemed to occur between baseline and two years, after which time tracer uptake appeared to decline in parallel. It has been suggested that this may reflect a confounding pharmacological effect of the treatment on the uptake of [^{123}I]β-CIT. Furthermore, when the identical two-year data were reported in an earlier publication, there was no difference in the rate of decline of [^{123}I]β-CIT uptake between the two groups[11]. This disparity was thought to perhaps reflect an interval change in the method used to reconstruct the scans.

In the REAL-PET study, 6FD uptake was measured at baseline and after two years of treatment in PD patients who were randomized to receive either levodopa or ropinirole. 6-[^{18}F]fluoro-L-dopa (6FD) uptake declined at a significantly faster rate in the levodopa treated group than in those patients who were treated with the dopamine agonist. As was also the case in the CALM-PD study, however, clinical evaluations of parkinsonism (performed with patients on medication) favoured levodopa treatment, although the incidence of dyskinesias was much lower in the ropinirole treated group[91] (see discussion by Dr. Miyasaki for details). An important methodological distinction between this and the CALM-PD study was the delay of the baseline scan until after active treatment had been initiated, an attempt to minimize the confound arising from potential effects of medication on tracer uptake.

Although both the CALM-PD and REAL-PET studies suggested on the basis of imaging outcomes that the rate of disease progression was slower when treatment was initiated with a dopamine agonist, the clinical measures did not substantiate this and most neurologists remain unconvinced. Detailed analyses of the results and potential confounds are provided elsewhere.[92,93]

Two other recent observations have cast further doubt on the utility of functional imaging measures for the assessment of disease modifying treatments. In the ELLDOPA study (as discussed by Dr. Suchowersky), three doses of levodopa were compared to a placebo. Medications were then withdrawn for two weeks and disease progression over 40 weeks was assessed based on clinical measures. Somewhat unexpectedly, there was a dose-dependent effect in which the rate of clinical decline was apparently lower in patients treated with levodopa.[5] Although this could be interpreted as evidence of neuroprotection by levodopa, possibly a more likely explanation is inadequate washout, even after two weeks. The issue of concern here is that the imaging data using [^{123}I]β-CIT SPECT once again were in complete conflict with the clinical observations. The imaging studies suggested a dose dependent increase in the rate of decline of [^{123}I]β-CIT uptake, when analysis was confined to subjects with abnormal uptake at baseline (i.e. subjects with normal scans at baseline were excluded – see below).

Another source of concern comes from recent studies of fetal transplantation for PD. In one of these, the clinical benefits were at best modest, while PET showed robust improvements in 6FD uptake.[94] In the second study, there was no significant improvement in motor function at two years, while PET showed a sustained and substantial improvement in 6FD uptake, albeit to subnormal levels.[95]

Finally, each of the early treatment studies discussed above (CALM-PD, REAL-PET, ELLDOPA) showed a surprisingly high (close to 15%) incidence of people who had been diagnosed with PD but in whom imaging was normal. The meaning of this phenomenon (referred to as SWEDD, or Scans Without Evidence of Dopaminergic Deficit) is as yet unresolved. However, follow-up imaging in these patients shows no evidence of progression, suggesting that they represent an entirely different patient category from typical PD. Some of these patients may have been misdiagnosed and may suffer from essential tremor, an error that is fairly easy to make, particularly in early stages of disease. Others may have a form of parkinsonism unrelated to dopamine deficiency. Tremor-predominant PD may reflect serotonergic more than dopaminergic abnormalities,[96] although even patients with isolated resting tremor typically demonstrate functional imaging changes compatible with dopamine deficiency.

Taking these sobering observations together, should one conclude that functional imaging should be discarded as a meaningful outcome measure to determine the effects of disease modifying therapies? At this time, such a conclusion would be unduly harsh and defeatist. A number of recent papers have examined the ideal requirements for a biomarker to assess disease progression in PD.[97,98] Although positron emission tomography (PET) or SPECT may satisfy the majority of the proposed criteria, there is still uncertainty over whether changes are specific to the outcome of interest (in this case loss of

dopaminergic neurons), or whether other factors (such as compensatory changes or medications) might modify the measurement. It appears clear that 6FD, DAT ligands and DTBZ do not decline to exactly the same degree in PD[85]. This may reflect compensatory downregulation of the DAT and upregulation of L-aromatic amino acid decarboxylase, in an effort to maintain dopamine levels in the synapse. The effects of medication on the expression of these markers are unclear. While some authors have reported changes in DAT expression following a short course of dopaminergic therapy in PD,[99,100] this is inconsistent, and it has been difficult to demonstrate changes in 6FD uptake in response to medications.[101] DTBZ may be advantageous in this respect, as the VMAT2 appears to be relatively resistant to the effects of medication.[102-104]

Clinicians will understandably be hesitant to accept an effect of a therapeutic intervention that can be demonstrated on a test only, if there is no clinical correlate. However, it should be remembered that the clinical outcomes employed may also be suboptimal. Thus, the UPDRS Motor scale may be unduly influenced by measures of tremor or rigidity, whereas a measure that focuses entirely on bradykinesia may provide the best marker of dopaminergic deficiency.[105]

List of Participants

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EXHIBIT F

Newron

Newron Pharmaceuticals S.p.A.

Investor and analyst call

Safinamide

Study 018 Top-Line Results

November 4, 2010
03.00 p.m. CET

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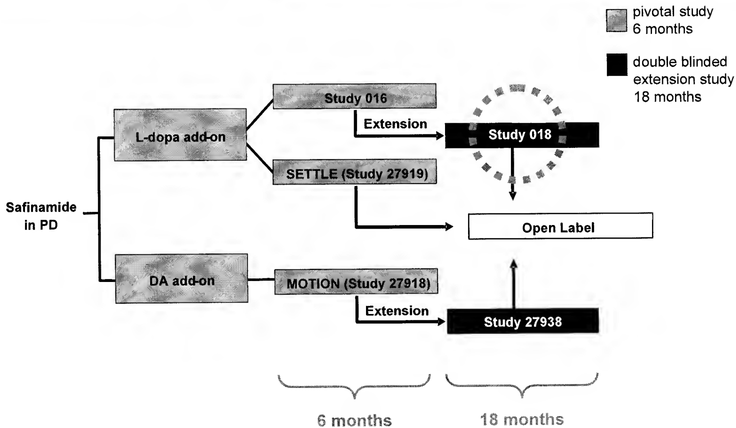
Safinamide Parkinson's disease - add-on program ongoing



Study 016 - Key inclusion criteria

- Male or female, aged 30-80 years
- Diagnosis of idiopathic Parkinson's Disease of > 3 yrs
- Levodopa responsive and receiving a stable dose of levodopa at screening
  - 4-10 doses per day
  - Any levodopa preparation (plus benserazide/carbidopa)
  - COMT inhibitors permitted (including Stalevo®)
- Patients may be receiving concomitant treatment with stable doses of a dopamine agonist and/or an anticholinergic
- Motor fluctuations with >1.5 hours OFF time during day
- Ability to maintain diary (18 hours) with help of caregiver
- Complete ophthalmologic screening

Study 016 - Baseline subject demographics and disease characteristics

	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Mean age (years) (SD)	59.4 (9.41)	60.1 (9.67)	60.1 (9.19)
Gender Male (%)	72.1%	70.4%	72.8%
Race			
Asian	180 (81.1%)	180 (80.7%)	179 (79.9%)
White	42 (18.9%)	43 (19.3%)	45 (20.1%)
At least one concomitant medical condition/illness	165 (74.3%)	178 (79.8%)	175 (78.1%)

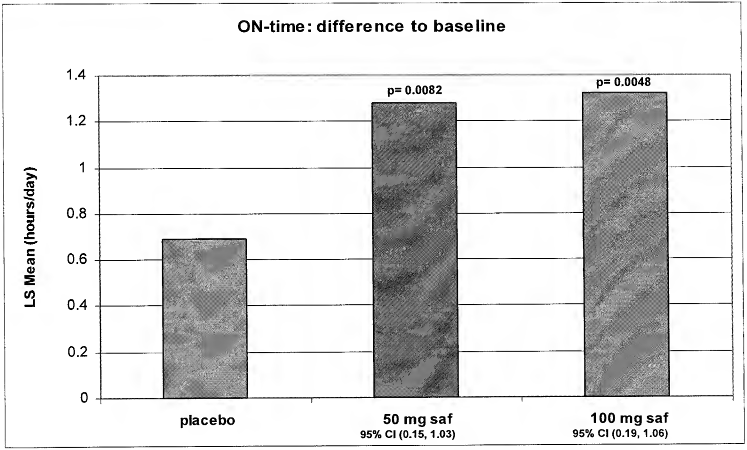
Study 016 – Parkinson's disease baseline characteristics

Newron

	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Baseline OFF time (hours) (SD)	5.3 (2.06)	5.2 (2.08)	5.2 (2.16)
Baseline ON time (hours) (SD)	9.30 (2.155)	9.37 (2.259)	9.52 (2.426)
Baseline UPDRS Part III ON (SD)	28.7 (12.03)	27.3 (12.67)	28.3 (13.30)
% of patients with Troublesome Dyskinesia (≥ 30 mins)	32.8 %	32.3 %	29.5 %
PD Treatment			
Levodopa	222 (100.0%)	223 (100.0%)	224 (100.0%)
Dopamine Agonist	136 (61.3%)	142 (63.7%)	128 (57.1%)
Anticholinergic	86 (38.7%)	73 (32.7%)	85 (37.9%)
Entacapone	56 (25.2%)	52 (23.3%)	55 (24.65)
Stalevo	33 (14.9%)	30 (13.5%)	36 (16.1%)
Amantadine	32 (14.4%)	29 (13.0%)	30 (13.4%)

Study 016 primary endpoint met : ON Time

Study qualified pivotal study



p-values were calculated using a mixed linear model based on the change from baseline with baseline as covariate

Study 018 objective:

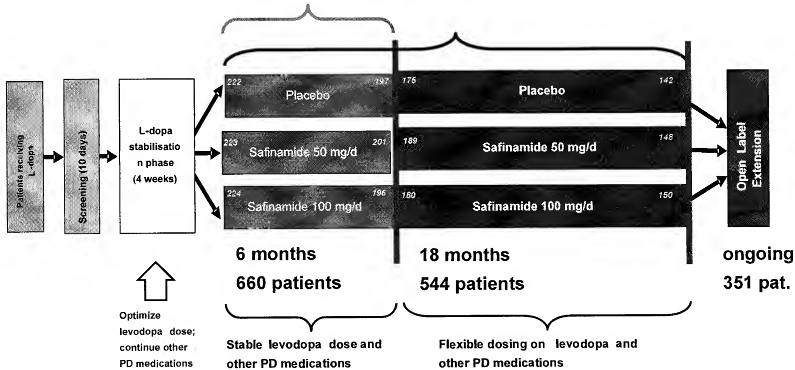
Long-term safety and efficacy for mid-to-late stage Parkinson's disease

Newron

- A double-blind, placebo controlled 18 months extension study of phase 3 pivotal study 016 (study 018 is not a pivotal study)
- To assess 2 year safety and efficacy of 50 and 100 mg safinamide/day as add-on therapy to stable L-dopa in PD patients with motor fluctuations

Study design 016 and 018

Double-blind, placebo controlled study through 2 years



Study 018 - Secondary endpoints

- Change in "On-time" (ON + ON with minor dyskinesia) from baseline of study 016
- Change in individual diary categories compared to baseline of study 016
  - Improvement in ON time + ON time with minor dyskinesia with no increase in troublesome dyskinesia with respect to the 016 baseline
  - Lack of worsening (≤ 30 mins) in ON time + ON time with minor dyskinesia with no increase in troublesome dyskinesia with respect to the 016 baseline
- Diary responder rate at 12-, 18-, and 24-months on the ITT and mITT, and on those who completed 24 months treatment period)
- UPDRS part IV (total and dyskinesia sub-items 32-35 and 32-24)
- Time to develop troublesome dyskinesia (≥ 30 minutes increase compared to baseline)
- Time to develop any (minor + troublesome) dyskinesia (≥ 30 minutes increase compared to baseline)
- Change in ADLs during ON-time (UPDRS part II) compared to placebo
- Maintenance of effects in UPDRS part II responders (≥ 20% improvement from baseline to 016 endpoint)
- Percentage of change in L-dopa dose
- Percentage of change in any anti-PD dose
- Change in motor symptoms (UPDRS part III)
- CGI – change from baseline – mean score in the course of the study
- CGI – severity of illness – mean change from baseline to endpoint

Study 016/018 – Parkinson's disease baseline characteristics

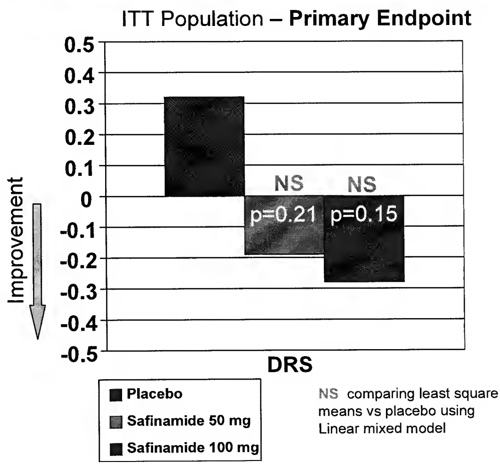
	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Baseline OFF time (hours) (SD)	5.3 (2.06)	5.2 (2.08)	5.2 (2.16)
Baseline ON time (hours) (SD)	9.30 (2.155)	9.37 (2.259)	9.52 (2.426)
Baseline UPDRS Part III ON (SD)	28.7 (12.03)	27.3 (12.67)	28.3 (13.30)
% of patients with Troublesome Dyskinesia (≥ 30 mins)	32.8 %	32.3 %	29.5 %
PD Treatment			
Levodopa	222 (100.0%)	223 (100.0%)	224 (100.0%)
Dopamine Agonist	136 (61.3%)	142 (63.7%)	128 (57.1%)
Anticholinergic	86 (38.7%)	73 (32.7%)	85 (37.9%)
Entacapone	56 (25.2%)	52 (23.3%)	55 (24.65)
Stalevo	33 (14.9%)	30 (13.5%)	36 (16.1%)
Amantadine	32 (14.4%)	29 (13.0%)	30 (13.4%)

Source reference: Tables 30.1 - 33 -25.3 - 12.2

Dyskinesia Rating Scale (DRS)

Primary endpoint not met - Sub-sequential pre-specified endpoints considered as exploratory

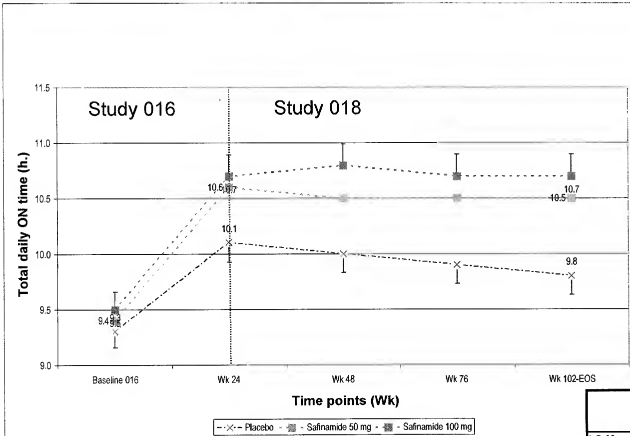
After 24 months, non-statistically significant mean improvements of 0.19 and 0.28 in the DRS score were observed in patients who received safinamide 50 mg and 100 mg respectively, versus a worsening of 0.32 for the placebo group (respectively p=0.21 and p=0.15 versus placebo)



Main secondary endpoint: ON time

(primary endpoint 016)

Maintained clinical effect over 2 years (exploratory analysis)



	Safinamide 50 mg/day	Safinamide 100 mg/day
LS Mean	1.01	1.18
LS Diff vs Placebo	0.67	0.83
95% CI of LS Diff	(0.23,1.11)	(0.39,1.27)
p-value vs Placebo	0.0031	0.0002

Additional secondary endpoints

- Significant benefit of the 100 mg/day dose on:
  - Activities of daily living (UPDRS II)
  - Motor symptoms (UPDRS III)
  - Complications of dopaminergic treatment (UPDRS IV)
  - Symptoms of depression (GRID HAMD)
  - Quality of life (PDQ-39)

  at the two year-endpoint

- Full study results will be submitted for presentation at upcoming scientific meetings

Study 018 supports safety profile of safinamide on long-term

Newron

Adverse Events

- Serious adverse events, clinically notable events among both treatment groups in the study (50 mg and 100 mg/d) were comparable with those in the placebo group

Drop Outs

- There were approx. 80% completers across the 3 groups

Prospect

- These long-term treatment results are encouraging because they support the safety profile of safinamide and results of an exploratory analysis of its effect on motor function were consistent with the effect observed in the six-month study in this advanced Parkinson's disease population
- These results may offer new hope to patients with Parkinson's disease as they need to take medications for long periods of time
- The effect of safinamide on dyskinesia will be further explored in an ongoing dedicated pilot study

EXHIBIT G

Chap. 372

PARKINSON'S DISEASE AND OTHER MOVEMENT DISORDERS

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PARKINSON'S DISEASE AND RELATED DISORDERS

Parkinson's disease (PD) is the second commonest neurodegenerative disease, exceeded only by Alzheimer's disease (AD). It is estimated that approximately one million persons in the United States and five million persons in the world suffer from this disorder. PD affects men and women of all races, all occupations, and all countries. The mean age of onset is about 60 years, but cases can be seen in patients in their 20s, and even younger. The frequency of PD increases with aging, and based on projected population demographics it is estimated that the prevalence will dramatically increase in future decades.

Clinically, PD is characterized by rest tremor, rigidity, bradykinesia, and gait impairment, known as the "cardinal features" of the disease. Additional features can include freezing of gait, postural instability, speech difficulty, autonomic disturbances, sensory alterations, mood disorders, sleep dysfunction, cognitive impairment and dementia (Table 372-1), known as non-dopaminergic features because they do not fully respond to dopaminergic therapy.

Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra par compacta (SNc), reduced striatal dopamine, and intracytoplasmic proteinaceous inclusions known as Lewy bodies (Figure 372-1). While interest has primarily focused on the dopamine system, neuronal degeneration with inclusion body formation can also affect cholinergic neurons of the nucleus basalis of Meynert (NBM), norepinephrine neurons of the locus coeruleus (LC), serotonin neurons in the raphe nuclei of the brain stem, and neurons of the olfactory system, cerebral hemispheres, spinal cord, and peripheral autonomic nervous system. This "non-dopaminergic" pathology is likely responsible for the "non-dopaminergic" clinical features listed in Table 372-1. Indeed, there is evidence that pathology begins in the peripheral autonomic nervous system, olfactory system, and dorsal motor nucleus of the vagus nerve in the lower brain stem, and then spreads in a sequential manner to affect the upper brain stem and cerebral hemispheres. These studies suggest that dopamine neurons are affected in mid-stage disease. Indeed, several studies suggest that symptoms reflecting non-dopaminergic degeneration such as constipation, anosmia, REM behavior sleep disorder and cardiac denervation precede the onset of the classic motor features of the illness.

Differential diagnosis

Parkinsonism is a general term that is used to define a symptom complex manifest by bradykinesia with rigidity and/or tremor. It has a wide differential diagnosis (Table 372-2), and can reflect damage to different components of the basal ganglia. The basal ganglia comprise a group of subcortical nuclei that include the striatum (putamen and caudate nucleus), subthalamic nucleus (STN), globus pallidus pars externa (GPe), globus pallidus

pars interna (GPi) and the SNc (Figure 372-2). The basal ganglia play an important role in regulating normal motor behavior. It is now appreciated that basal ganglia also play a role in modulating emotional and cognitive functions. Among the different forms of parkinsonism, PD is the most common (approximately 75% of cases). Historically, PD was diagnosed based on the presence of two of three parkinsonian features (tremor, rigidity, bradykinesia). However, post mortem studies found a 24% error rate when these criteria were used. Clinicopathologic correlation studies subsequently determined that parkinsonism associated with rest tremor, asymmetry, and a good response to levodopa was more likely to predict the correct pathological diagnosis. With these revised criteria (known as the UK brain bank criteria) the clinical diagnosis of PD is confirmed pathologically in 99% of cases.

Imaging of the brain dopamine system in PD with positron emission tomography (PET) or single photon emission computerized tomography (SPECT) shows reduced uptake of striatal dopaminergic markers, particularly in the posterior putamen (Figure 372-3). Imaging can be useful in difficult cases or research studies, but is rarely necessary in routine practice as the diagnosis can usually be established on clinical criteria alone. This may change in the future when there is a disease-modifying therapy and it is important to make the diagnosis at as early a time point as possible. Genetic testing is not generally employed at present, but can be helpful for identifying at-risk individuals in a research setting. Mutations of the LRRK2 gene (see below) have attracted particular interest as they are the commonest cause of familial PD, and are responsible for approximately 1% of typical sporadic cases of the disease. Mutations in LRKK2 are particularly common causes of PD in Ashkenazi Jews and North African Berber Arabs.

The penentrance of the most common LRRK2 mutation ranges from 28 to 74% depending on age. Mutations in the parkin gene should be considered in patients with disease onset prior to 40 years.

Atypical and secodary parkinsonism

Atypical parkinsonism refers to a group of neurodegenerative conditions that usually are associated with more widespread neurodegeneration than is found in PD (often involvement of SNc and striatum and/or pallidum). As a group, they present with a parkinsonism (rigidity and bradykinesia) but typically have a slightly different clinical picture than PD, reflecting differences in underlying pathology. Parkinsonism in these conditions is often characterized by early speech and gait impairment, absence of rest tremor, no asymmetry, poor or no response to levodopa, and an aggressive clinical course. In the early stages, they may show some modest benefit from levodopa and be difficult to distinguish from PD. Neuroimaging of the dopamine system is usually not helpful, as several atypical parkinsonisms also have degeneration of dopamine neurons. Pathologically neurodegeneration occurs without Lewy bodies (see below for individual conditions). Metabolic imaging of the "basal ganglia/thalamus network" may be helpful, reflecting a pattern of decreased activity in the GPi with increased activity in the thalamus, the reverse of what is seen in PD.

Multiple system atrophy (MSA) manifests as a combination of parkinsonian, cerebellar, and autonomic features and can be divided into a predominant parkinsonian (MSA-p) or cerebellar (MSA-c) form. Clinically, MSA is suspected when a patient presents with atypical parkinsonism in conjunction with cerebellar signs and/or early and

prominent autonomic dysfunction, usually orthostatic hypotension (Chap. 375). Pathologically MSA is characterized by degeneration of the SNc, striatum, cerebellum and inferior olivary nuclei coupled with characteristic glial cytoplasmic inclusions (GCI) that stain for alpha synuclein. MRI can show pathologic iron accumulation in the striatum on T2-weighted scans, high signal change in the region of the external surface of the putamen (putaminal rim) in MSA-p, or cerebellar and brainstem atrophy (the pontine "hot cross buns" sign) in MSA-c.

Progressive supranuclear palsy (PSP) is a form of atypical parkinsonism that is characterized by slow ocular saccades, eyelid apraxia, and restricted eye movements with particular impairment of downward gaze. Patients frequently experience hyperextension of the neck with early gait disturbance and falls. In later stages, speech and swallowing difficulty and dementia become evident. MRI may reveal a characteristic atrophy of the midbrain with relative preservation of the pons (the "hummingbird sign" on midsagittal images). Pathologically, PSP is characterized by degeneration of the SNc and pallidum along with neurofibrillary tangles and GCIs that stain for tau.

Corticobasal ganglionic degeneration is less common and is usually manifest by asymmetric dystonic contractions and clumsiness of one hand coupled with cortical sensory disturbances manifest as apraxia, agnosia, focal myoclonus, or alien limb phenomenon (where the limb assumes a position in space without the patient being aware of it). Dementia may occur at any stage of the disease. MRI frequently shows asymmetric cortical atrophy. Pathological findings include achromatic neuronal degeneration with tau deposits similar to those found in PSP.

Secondary parkinsonism can be associated with drugs, stroke, tumor, infection, or exposure to toxins such as carbon monoxide or manganese. Dopamine blocking agents such as the neuroleptics are the commonest cause of secondary parkinsonism. These drugs are most widely used in psychiatry, but physicians should be aware that drugs such as metoclopramide and chlorperazine which are primarily used to treat gastrointestinal problems are also neuroleptic agents and common causes of secondary parkinsonism and tardive dyskinesia. Other drugs that can cause secondary parkinsonism include tetrabenazine, amiodarone and lithium.

Finally, parkinsonism can be seen as a feature of other degenerative disorders such as Wilson's disease, Huntington's disease (especially the juvenile form known as Westphall variant), dopa-responsive dystonia, and neurodegenerative disorders with brain iron accumulation such as pantothenate kinase (PANK)-associated neurodegeneration (formerly known as Hallervorden Spatz disease).

Some features that suggest parkinsonism might be due to a condition other than PD are shown in table 372-3.

Etiology and Pathogenesis

Most PD cases occur sporadically (~85-90%) and are of unknown cause. Twin studies suggest that environmental factors likely play the more important role in patients older than 50 years, with genetic factors being more important in younger patients. Epidemiologic studies suggest increased risk with exposure to pesticides, rural living and drinking well water and reduced risk with cigarette smoking and caffeine. However, no environmental factor has yet been determined to cause PD. The environmental hypothesis

received a boost with the demonstration in the 1980s that MPTP, a byproduct of the illicit manufacture of a heroin-like drug, caused a PD-like syndrome in addicts in northern California. MPTP is transported to the central nervous system where it is metabolized by to form MPP^+, a mitochondrial toxin which is selectively taken up by, and damages, dopamine neurons. However, MPTP or MPTP-like compounds have not been linked to sporadic PD. MPTP has, however, proven useful for generating an animal model of the disease. About 10-15% of cases are familial in origin, and multiple specific mutations and gene associations have been identified (Table 372-4). It has been proposed that most cases of PD are due to a "double hit" involving an interaction between a gene mutation that induces susceptibility coupled with exposure to a toxic environmental factor. In this scenario both factors are required for PD to ensue, while the presence of either one alone is not sufficient to cause the disease.

Factors that have been implicated in the pathogenesis of cell death include oxidative stress, intracellular calcium accumulation with excitotoxicity, inflammation, mitochondrial dysfunction and proteolytic stress. Whatever the pathogenic mechanism, cell death appears to occur, at least in part, by way of a signal-mediated apoptotic or "suicide" process. Each of these mechanisms offer potential targets for neuroprotective drugs. However, it is not clear which of these factors is primary, if the cause is the same in each case, or if one or all merely represent epiphenomena unrelated to the true cause of cell death that remains undiscovered (Figure 372-4).

Gene mutations discovered to date have been helpful in pointing to specific pathogenic mechanisms as being central to the neurodegenerative process. The most significant of these mechanisms appear to be protein misfolding and accumulation, and

mitochondrial dysfunction. The idea that proteins are involved in the pathogenesis of PD is not surprising, given that PD is characterized by Lewy bodies and Lewy neurites which are comprised of misfolded and aggregated proteins (Figure 372-1). Protein accumulation could result from either increased formation or impaired clearance of proteins. Mutations in alpha synuclein promote misfolding of the protein and the formation of oligomers and aggregates thought to be involved in the cell death process. Importantly, triplication of the wild type alpha synuclein gene can itself cause PD, indicating that increased production of even a normal protein can cause PD. Increased levels of unwanted proteins could also result from impaired clearance. Proteins are normally cleared by the ubiquitin proteasome system or the autophagy/lysosome pathway. These pathways are defective in patients with sporadic PD, and interestingly alpha synuclein is a prominent component of Lewy bodies in these cases. Further, mutations in parkin (a ubiquitin ligase which attaches ubiquitin to misfolded proteins to promote their transport to the proteasome for degradation) and UCH-L1 (which cleaves ubiqitin from misfolded proteins to permit their entry into the proteasome) are causative in other cases of familial PD. Collectively, these findings implicate abnormal protein accumulation in the etiology of PD. Indeed, in laboratory models both over-expression of alpha synuclein or impairment of proteasomal clearance mechanisms leads to degeneration of dopamine neurons with inclusion body formation.

Mitochondrial dysfunction has also been implicated in familial PD. Several causative genes (parkin, PINK1 and DJ1), either localize to mitochondria, and/or cause mitochondrial dysfunction in transgenic animals. Post-mortem studies have also shown a defect in complex I of the respiratory chain in the SNc of patients with sporadic PD.

Six different LRRK2 mutations have been linked to PD, with the Gly2019Ser being the commonest. The mechanism responsible for cell death with this mutation is not known but is thought to involve altered kinase activity.

Mutations in the glucocerebrosidase (GBA) gene associated with Gaucher's dsease are also associated with an increased risk of idiopathic PD. Again the mechanism is not precisely known, but it is noteworthy that it Gaucher's disease is associated with altered autophagy and lysosomal function, suggesting that mutations in this gene might also impair protein clearance leading to PD.

Whole genome association studies have provided conflicting results. Most recently, linkage to mutations in HLA genes were identified in PD patients suggesting that altered immunity or inflammation may be a causative or contributory factor.

While gene mutations account for only a small percentage of cases of PD, it is hoped that better understanding of the mechanisms whereby they cause cell death will provide insight into the nature of the cell death process in the more common sporadic form of the disease. These mutations could also permit the development of more relevant animal models of PD in which to test putative neuroprotective drugs.

Pathophysiology of PD

The classic model of basal ganglia functional organization in the normal and PD states is provided in Figure 372-5. A series of neuronal loops link the basal ganglia nuclei with corresponding cortical motor regions in a somatotopic manner to help regulate motor function. The striatum is the major input region of the basal ganglia, while the GPi and SNr are the major output regions. The input and output regions are connected via direct

and indirect pathways which have reciprocal effects on the output pathway. The output of the basal ganglia provides inhibitory tone to thalamic and brain stem neurons which in turn connect to motor systems in the cerebral cortex and spinal cord to regulate motor function. Dopaminergic projections from SNc neurons serve to modulate neuronal firing and to stabilize the basal ganglia network.

In PD, dopamine denervation leads to increased firing of neurons in the STN and GPi resulting in excessive inhibition of the thalamus, reduced activation of cortical motor systems and the development of parkinsonian features (Figure 372-5). The current role of surgery in the treatment of PD is based upon this model, which predicted that lesions or high frequency stimulation of the STN or GPi might reduce this neuronal overactivity and improve PD features.

Treatment of PD

Levodopa

Since its introduction in the late 1960s, levodopa has been the mainstay of therapy for PD. Experiments in the late 1950s by Carlsson demonstrated that blocking dopamine uptake with reserpine caused rabbits to become parkinsonian; this could be reversed with the dopamine precursor, levodopa. Subsequently, Hornykiewicz demonstrated a dopamine deficiency in the striatum of PD patients, and suggested the potential benefit of dopaminergic replacement therapy. Dopamine does not cross the blood brain barrier (BBB), so clinical trials were initiated with levodopa, a precursor of dopamine. Studies over the course of the next decade confirmed the value of levodopa and revolutionized the treatment of PD.

Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea and vomiting due to activation of dopamine receptors in the area postrema which are not protected by the BBB. In the United States levodopa is combined with the decarboxylase inhibitor carbidopa (Sinemet®), while in many other countries it is combined with benserazide (Madopar®). Levodopa is also available in controlled release formulations as well as in combination with a COMT inhibitor (see below). Levodopa remains the most effective symptomatic treatment for PD, and the gold standard against which new therapies are compared. No current medical or surgical treatment provides anti-parkinsonian benefits superior to what can be achieved with levodopa. Levodopa benefits the classic motor features of PD, prolongs independence and employability, improves quality of life, and increases life span. Almost all PD patients experience improvement, and failure to respond to an adequate trial should cause the diagnosis to be questioned.

There are, however, important limitations of levodopa therapy. Acute dopaminergic side effects include nausea, vomiting, and orthostatic hypotension. These are usually transient, and can generally be avoided by gradual titration. If they persist, they can be treated with additional doses of a peripheral decarboxylase inhibitor (e.g. carbidopa) or a peripheral dopamine blocking agent such as domperidone (not available in the United States). More important are motor complications (see below) that develop in the majority of patients chronically treated with levodopa therapy. In addition, features such as falling, freezing, autonomic dysfunction, sleep disorders, and dementia may emerge that are not adequately controlled by levodopa. Indeed, these non-dopaminergic

features are the primary source of disability and main reason for nursing home placement for patients with advanced PD.

Levodopa-induced motor complications consist of fluctuations in motor response and involuntary movements known as dyskinesias (Figure 372-6). When patients initially take levodopa, benefits are long-lasting (many hours) even though the drug has a relatively short half-life (60-90 minutes). With continued treatment, however, the duration of benefit following an individual dose becomes progressively shorter until it approaches the half-life of the drug. This loss of benefit is known as the *wearing-off effect*. At the same time, many patients develop dyskinesias. These tend to occur at the time of maximal clinical benefit and peak plasma concentration (peak-dose dyskinesia). They are usually choreiform in nature, but can manifest as dystonia, myoclonus or other movement disorders. They are not troublesome when mild, but can be disabling when severe and can limit the ability to fully utilize levodopa to control PD features. In more advanced states patients may cycle between "on" periods complicated by disabling dyskinesias and "off" periods in which they suffer severe parkinsonism. Patients may also experience "diphasic dyskinesias" which occur as the levodopa dose begins to take effect and again as it wears off. These dyskinesias typically consist of transient, stereotypic, rhythmic movements that predominantly involve the lower extremities and are frequently associated with parkinsonism in other body regions. They can be relieved by increasing the dose of levodopa, although higher doses may induce more severe peak-dose dyskinesia.

The cause of levodopa-induced motor complications is not precisely known. They are more likely to occur in young individuals with severe disease and with higher doses

of levodopa. The classic model of the basal ganglia has been useful for understanding the origin of motor features in PD, but has proven less valuable for understanding levodopa-induced dyskinesias (Figure 372-4). The model predicts that dopamine replacement might excessively inhibit the pallidal output system thereby leading to increased thalamo-cortical activity, enhanced stimulation of cortical motor regions and the development of dyskinesia. However, lesions of the pallidum that completely destroy its output are associated with amelioration rather than induction of dyskinesia as suggested by the classic model. It is now thought that dyskinesia results from levodopa-induced alterations in the GPi neuronal firing frequency pattern (pauses, bursts, synchrony, etc.) and not simply the firing frequency alone. This in turn leads to the transmission of misinformation from pallidum to thalamus/cortex resulting in dyskinesia. Pallidotomy might thus ameliorate dyskinesia by blocking this abnormal firing pattern and preventing the transfer of mis-information to motor systems.

Current information suggests that altered neuronal firing patterns and motor complications relate to non-physiologic levodopa replacement. Striatal dopamine levels are normally maintained at a relatively constant level. In the PD state, dopamine neurons degenerate and striatal dopamine is dependent on peripheral availability of levodopa. Intermittent doses of short-acting levodopa do not restore dopamine in a physiologic manner and cause dopamine receptors to be exposed to alternating high and low concentrations of dopamine. This intermittent or pulsatile stimulation of dopamine receptors induces molecular changes in striatal neurons, and neurophysiologic changes in pallidal neurons leading to the development of motor complications. It has been hypothesized that more continuous delivery of levodopa might prevent the development

of motor complications. Indeed, continuous levodopa infusion is associated with improvement in both "off" time and dyskinesia in advanced PD patients, but this approach has not yet been proven to prevent dyskinesia in clinical trials.

Behavioral alterations can be encountered in levodopa-treated patients. A dopamine dysregulation syndrome has been described where patients have a craving for levodopa and take frequent and unnecessary doses of the drug in an addictive manner. PD patients taking high doses of levodopa can also have purposeless, stereotyped behaviors such as the meaningless assembly and disassembly or collection and sorting of objects. This is known as punding, a term taken from the Swedish description of the meaningless, behaviors seen in chronic amphetamine users. Hypersexuality and other impulse control disorders are occasionally encountered with levodopa, although these are more commonly seen with dopamine agonists.

Dopamine agonists

Dopamine agonists are a diverse group of drugs that act directly on dopamine receptors. Unlike levodopa, they do not require metabolism to an active product and do not undergo oxidative metabolism. Initial dopamine agonists were ergot derivatives (e.g. bromocriptine, pergolide, cabergoline) and were associated with ergot-related side effects including cardiac valvular damage. They have largely been replaced by a second generation of non-ergot dopamine agonists (e.g. pramipexole, ropinirole, rotigotine). In general, dopamine agonists do not have comparable efficacy to levodopa. They were initially introduced as adjuncts to levodopa to enhance motor function and reduce "off" time in fluctuating patients. Subsequently, it was shown that dopamine agonists, possibly because they are relatively long-acting, are less prone than levodopa to induce dyskinesia.

For this reason many physicians initiate therapy with a dopamine agonist, although supplemental levodopa is eventually required in virtually all patients. Both ropinirole and pramipexole are available as orally administered immediate (tid) and extended release (qd) formulations. Rotigotine is administered as a once-daily transdermal patch. Apomorphine is a dopamine agonist with efficacy comparable to levodopa, but it must be administered parenterally and has a very short half life and duration of activity (45 minutes). It is generally administered sc as a rescue agent for the treatment of severe "off" episodes, Apomorphine can also be administered by continuous infusion and has been demonstrated to reduce both off time and dyskinesia in advanced patients. However, infusions are cumbersome, and this approach has not been approved in the United States.

Acute side effects of dopamine agonists include nausea, vomiting, and orthostatic hypotension. As with levodopa, these can usually be avoided by slow titration. Hallucinations and cognitive impairment are more common with dopamine agonists than levodopa. Sedation with sudden unintended episodes of falling asleep while driving a motor vehicle have been reported. Patients should be informed about this potential problem and should not drive when tired. Injections of apomorphine and patch delivery of rotigotine can be complicated by development of skin lesions at sites of administration. Recently, it has become appreciated that dopamine agonists are associated with impulse control disorders including pathologic gambling, hypersexuality, and compulsive eating and shopping. The precise cause of these problems, and why they appear to occur more frequently with dopamine agonists than levodopa, remains to be resolved, but reward

systems associated with dopamine and alterations in the ventral striatum have been implicated.

MAO-B inhibitors

Inhibitors of monoamine oxidase type B (MAO-B) block central dopamine metabolism and increase synaptic concentrations of the neurotransmitter. Selegiline and rasagiline are relatively selective suicide inhibitors of the MAO-B enzyme. Clinically, MAO-B inhibitors provide modest anti-parkinsonian benefits when used as monotherapy in early disease, and reduced 'off' time when used as an adjunct to levodopa in patients with motor fluctuations. MAO-B inhibitors are generally safe and well tolerated. They may increase dyskinesia in levodopa-treated patients but this can usually be controlled by down-titrating the dose of levodopa. Inhibition of the MAO-A isoform prevents metabolism of tyramine in the gut leading to a potentially fatal hypertensive reaction known as a "cheese effect" as it can be precipitated by foods rich in tyramine such as some cheeses, aged meats, and red wine. Selegiline and rasagiline do not functionally inhibit MAO-A in doses employed in clinical practice, and are not associated with a "cheese reaction". There are theoretical risks of a serotonin reaction in patients receiving concomitant SSRI anti-depressants, but these are rarely encountered.

Interest in MAO-B inhibitors has also focused on their potential to have disease-modifying effects. MPTP toxicity can be prevented by co-administration of a MAO-B inhibitor that blocks its conversion to the toxic pyridinium ion MPP^+. MAO-B inhibitors also have the potential to block the oxidative metabolism of dopamine and prevent oxidative stress. In addition, both selegiline and rasagiline incorporate a propargyl ring within their molecular structure that provides anti-apoptotic effects in laboratory models.

The DATATOP study showed that selegiline significantly delayed the time until the emergence of disability necessitating the introduction of levodopa in untreated PD patients. However, it could not be determined whether this was due to a neuroprotective effect that slowed disease progression or a symptomatic effect that merely masked ongoing neurodegeneration. More recently, the ADAGIO study demonstrated that early-treatment with rasagiline 1mg per day but not 2 mg per day provided benefits that could not be achieved with delayed-treatment with the same drug, consistent with a disease modifying effect; however, the long-term significance of these findings is uncertain.

COMT inhibitors

When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized by catechol-O-methyltransferase (COMT). Inhibitors of COMT increase the elimination half life of levodopa and enhance its brain availability. Combining levodopa with a COMT inhibitor reduces "off" time and prolongs "on" time in fluctuating patients while enhancing motor scores. Two COMT inhibitors have been approved, tolcapone and entacpaone. There is also a combination tablet of levodopa, carbidopa, and entacapone (Stalevo®).

Side effects of COMT inhibitors are primarily dopaminergic (nausea, vomiting, increased dyskinesia) and can usually be controlled by down-titrating the dose of levodopa by 20-30%. Severe diarrhea has been described with tolcapone, and to a lesser degree with entacapone, and necessitates stopping the medication in 5-10% of individuals. Cases of fatal hepatic toxicity have been reported with tolcapone, and periodic monitoring of liver function is required. This problem has not been encountered with entacapone.

Discoloration of urine can be seen with both COMT inhibitors due to accumulation of a metabolite, but is of no clinical concern.

It has been proposed that initiating levodopa in combination with a COMT inhibitor to enhance its elimination half life will provide more continuous levodopa delivery and reduce the risk of motor complications. While this result has been demonstrated in parkinsonian monkeys, and continuous infusion reduces off time and dyskinesia in advanced patients, no benefit of initiating levodopa with a COMT inhibitor compared to levodopa alone was detected in early PD patients in the STRIDE-PD study, and the main value of COMT inhibitors for now continues to be in patients who experience motor fluctuations.

Other Medical Therapies

Central acting anticholinergic drugs such as trihexyphenidyl and benztropine were used historically for the treatment for PD, but lost favor with the introduction of dopaminergic agents. Their major clinical effect is on tremor, although it is not certain that this is superior to what can be obtained with agents such as levodopa and dopamine agonists. Still, they can be helpful in individual patients. Their use is limited particularly in the elderly, due to their propensity to induce a variety of side effects including urinary dysfunction, glaucoma, and particularly cognitive impairment.

Amantadine also has historical importance. Originally introduced as an anti-viral agent, it was appreciated to also have anti-parkinsonian effects that are now thought to be due to NMDA receptor antagonism. While some physicians use amantadine in patients with early disease for its mild symptomatic effects, it is most widely used as an anti-dyskinesia agent in patients with advanced PD. Indeed, it is the only oral agent that has been

demonstrated in controlled studies to reduce dyskinesia while improving parkinsonian features, although benefits may be relatively transient. Side effects include livido reticularis, weight gain, and impaired cognitive function. Amantadine should always be discontinued gradually as patients can experience withdrawal symptoms.

A list of the major drugs and available dosage strengths is provided in Table 372-5.

Neuroprotection

Despite the many therapeutic agents available for the treatment of PD, patients can still experience intolerable disability due to disease progression and the emergence of features such as falling and dementia that are not controlled with dopaminergic therapies. Trials of several promising agents such as selegiline, coenzme Q10, pramipexole, and ropinirole have had positive results in clinical trials consistent with disease-modifying effects. However, it is not possible to determine if the positive results are due to neuroprotection with slowed disease progression or confounding symptomatic or pharmacologic effects that mask ongoing progression. If it could be determined that a drug slowed disease progression, this would be a major advance in the treatment of PD.

Surgical treatment

Surgical treatments for PD have been employed for more than a century. Lesions placed in the motor cortex improved tremor, but were associated with motor deficits and this approach was abandoned. Subsequently, it was appreciated that lesions placed into the VIM nucleus of the thalamus reduced contralateral tremor without inducing hemiparesis, but these lesions did not meaningfully help other more disabling features of PD. Lesions placed in the GPi improved rigidity and bradykinesia as well as tremor, particularly if

placed in the posteroventral portion of the nucleus. Importantly, pallidotomy was also associated with marked improvement in contralateral dyskinesia. This procedure gained favor with greater understanding of the pathophysiology of PD (see above). However, this procedure is not optimal for patients with bilateral disease, as bilateral lesions are associated with side effects such as dysphagia, dysarthria and impaired cognition.

Most surgical procedures for PD performed today utilize deep brain stimulation (DBS). Here, an electrode is placed into the target area and connected to a stimulator inserted subcutaneously over the chest wall. DBS simulates the effects of a lesion without necessitating a brain lesion. The stimulation variables can be adjusted with respect to electrode configuration, voltage, frequency, and pulse duration in order to maximize benefit and minimize adverse side effects. In cases with intolerable side effects, stimulation can be stopped and the system removed. The procedure has the advantage that it does not require making a lesion in the brain and is thus suitable for performing bilateral procedures with relative safety.

DBS for PD primarily targets the STN and GPi. It provides dramatic results particularly with respect to off time and dyskinesias, but does not improve features that fail to respond to levodopa and does not prevent the development or progression of non-dopaminergic features such as freezing, falling and dementia. The procedure is thus primarily indicated for patients who suffer disability resulting from levodopa-induced motor complications that cannot be satisfactorily controlled with drug manipulation. Side effects can be seen with respect to the surgical procedure (hemorrhage, infarction, infection), the DBS system (infection, lead break, lead displacement, skin ulceration) or stimulation (ocular and speech abnormalities, muscle twitches, paresthesia, depression,

and rarely suicide). Recent studies indicate that benefits following DBS of the STN and GPi are comparable, but that GPi stimulation may be associated with a reduced frequency of depression. While not all PD patients are candidates, the procedure is profoundly beneficial for many. Research studies are currently examining additional targets that might benefit gait dysfunction, depression and cognitive impairment in PD patients.

Experimental Surgical Therapies for PD

There has been considerable scientific and public interest in a number of novel therapies as possible treatments for PD. These include cell-based therapies (such as transplantation of fetal nigral dopamine cells or dopamine neurons derived from stem cells), gene therapies, and trophic factors. Transplant strategies are based on implanting dopaminergic cells into the striatum to replace degenerating SNc dopamine neurons. Fetal nigral mesencephalic cells have been demonstrated to survive implantation, reinnervate the striatum in an organotypic manner, and restore motor function in PD models. Several open-label studies reported positive results. However, two double-blind, sham surgery-controlled studies failed to show significant benefit of fetal nigral transplantation in comparison to a sham operation with respect to their primary endpoints. Post hoc analyses showed possible benefits in patients < 60 years and in those with milder disease. It is now appreciated that grafting of fetal nigral cells is associated with a previously unrecognized form of dyskinesia that persists even after lowering or stopping levodopa. In addition, there is evidence that after many years, transplanted healthy embryonic dopamine neurons from unrelated donors can develop PD pathology, suggesting that they somehow became affected by the disease process. Most importantly, it is not clear how replacing dopamine cells alone will improve non-dopaminergic features such as falling

and dementia which are the major sources of disability for advanced patients. These same concerns apply to dopamine neurons derived from stem cells, which have not yet been tested in PD patients and bear the additional theoretical concern of unanticipated side effects such as tumors. The short-term future for this technology as a treatment for PD, at least in its current state, is therefore not promising.

Gene therapy involves viral vector delivery of the DNA of a therapeutic protein to specific target regions. The DNA of the therapeutic protein can then be incorporated into the genome of host cells and thereby, in principle, provide continuous and long-lasting delivery of the therapeutic molecule. The AAV2 virus has been most often used as the viral vector because it does not promote an inflammatory response, is not incorporated into the host genome, and is associated with long-lasting transgene expression. Studies performed to date in PD have delivered aromatic amino acid decarboxylase (AADC) with or without tyrosine hydroxylase to the striatum to facilitate dopamine production; glutamic acid decarboxylase (GAD) to the STN to inhibit overactive neuronal firing in this nucleus; and trophic factors such as GDNF and neurturin to the striatum to enhance and protect residual dopamine neurons in the SNc by way of retrograde transmission. Positive results have been reported with open label studies, but these have not yet been confirmed in double blind trials. While gene delivery technology has great potential, this approach also carries the risk of possible unanticipated side effects, and current approaches also do not address the non-dopamine features of the illness.

Management of the non-motor and non-dopaminergic features of PD

While most attention has focused on the dopaminergic features of PD, management of the non-dopaminergic features of the illness should not be ignored. Some non-motor features,

while not thought to reflect dopaminergic pathology, nonetheless benefit from dopaminergic drugs. For example problems such as anxiety, panic attacks, depression, sweating, sensory problems, freezing, and constipation all tend to be worse during off periods and improved with better dopaminergic control of the underlying PD state. Approximately 50% of PD patients suffer depression during the course of the disease that is frequently underdiagnosed and undertreated. Anti-parkinsonian agents can help, but antidepressants should not be withheld particularly for patients with major depression. Serotonin syndromes have been a theoretical concern with the combined use of SSRIs and MAO-B inhibitors, but are rarely encountered. Anxiety can be treated with short-acting benzodiazepines.

Psychosis can be a major problem in PD. In contrast to AD, hallucinations are typically visual, formed, and non-threatening, and can limit the use of dopaminergic agents to adequately control PD features. Psychosis in PD often responds to low doses of atypical neuroleptics. Clozapine is the most effective, but can be associated with agranulocytosis and regular monitoring is required. For this reason many physicians start with quetiapine even though it is not as effective as clozapine in controlled trials. Hallucinations in PD patients are often a harbinger of a developing dementia.

Dementia in PD (PDD) is common, affecting as many as 80% of patients. Its frequency increases with aging, and in contrast to AD, primarily affects executive functions and attention with relative sparing of language, memory and calculations. PDD is the commonest cause of nursing home placement for PD patients. When dementia precedes, or develops within one year after, the onset of motor dysfunction it is by convention referred to as Dementia with Lewy Bodies (DLB; Chap. 371). These patients are

particularly prone to have hallucinations and diurnal fluctuations. Pathologically, DLB is characterized by Lewy bodies distributed throughout the cerebral cortex (especially the hippocampus and amygdala). It is likely that DLB and PDD represent a PD spectrum rather than separate disease entities. Levodopa and other dopaminergic drugs can aggravate cognitive function in demented patients and should be stopped or reduced to try and provide a compromise between anti-parkinsonian benefit and preserved cognitive function. Drugs are usually discontinued in the following sequence; anticholinergics, amantadine, dopamine agonists, COMT inhibitors, and MAO-B inhibitors. Eventually patients with cognitive impairment should be managed with the lowest dose of standard levodopa that provides meaningful anti-parkinsonian effects and does not aggravate mental function. Anti-cholinesterase agents such as rivastigmine and donepezil reduce the rate of deterioration of measures of cognitive function in controlled studies, and can improve attention. Memantine, an antiglutamatergic agent, may also provide benefit for some PDD patients.

Autonomic disturbances are common and frequently require attention. Orthostatic hypotension can be problematic and contribute to falling. Initial treatment should include adding salt to the diet and elevating the head of the bed to prevent overnight sodium naturesis. Low doses of florinef or midodrine control most cases. Vasopressin, erythropoetin and the norepinephrine precursor 3-0-methylDOPS can be used in severe cases. If orthostatic hypotension is prominent in early disease, MSA should be considered. Sexual dysfunction can be helped with sildenafil or tadalafil. Urinary problems, especially in males, should be treated in consultation with a urologist to exclude prostate problems. Cholinergic agents such as ditropan that promote bladder

contraction may be helpful. Constipation can be a very important problem for PD patients. Mild laxatives can be useful, but physicians should first ensure that patients are drinking adequate amounts of fluid and consuming a diet rich in bulk with green leafy vegetables and bran. Agents that promote GI motility can also be helpful.

Sleep disturbances are common in PD patients, with many experiencing fragmented sleep with excess daytime sleepiness. Restless leg syndrome, sleep apnea, and other sleep disorders should be treated as appropriate. REM behavior disorder (RBD) may precede the onset of motor features. This syndrome is comprised of violent movements and vocalizations during REM sleep, possibly representing acting out of dreams due to a failure of the normal inhibition of motor movements that typically accompanies REM sleep. Low doses of clonazepam are usually effective in controlling this problem. Consultation with a sleep specialist and polysomnography may be necessary to identify and optimally treat sleep problems.

Non-pharmacologic therapy

Gait dysfunction with falling is an important cause of disability in PD. Dopaminergic therapies can help patients whose gait is worse in off time, but there are currently no specific therapies available. Canes and walkers may become necessary.

Freezing episodes, where patients freeze in place for seconds to minutes, are another cause of falling. Freezing during off periods may respond to dopaminergic therapies, but there are no specific treatments for on period freezing. Some patients will respond to sensory cues such as marching in place, singing a song,or stepping over an imaginary line.

Exercise, with a full range of active and passive movements, has been shown to improve and maintain function for PD patients. It is less clear that formal physical therapy is necessary, unless there is a specific indication. It is important for patients to maintain social and intellectual activities to the extent possible. Education, assistance with financial planning, social services and attention to home safety are important elements of the overall care plan. Information is available through numerous PD foundations and on the web, but should be reviewed with physicians to ensure accuracy. The needs of the caregiver should not be neglected. Caring for a person with PD involves a substantial work effort and there is an increased incidence of depression among caregivers. Support groups for patients and caregivers may be useful.

Current Management of PD

The management of PD should be tailored to the needs of the individual patient and there is no single treatment approach that is universally accepted. Clearly, if an agent could be demonstrated to have disease-modifying effects it should be initiated at the time of diagnosis. Indeed, constipation, REM behavior disorder, and anosmia may represent pre-motor features of PD and could permit the initiation of a disease-modifying therapy even prior to onset of the classical motor features of the disease. However, no therapy has yet been proven to be disease-modifying. For now, physicians must use their judgment in deciding whether or not to introduce rasaligine (see above) or other drugs for their possible disease-modifying effects.

The next important issue to address is when to initiate symptomatic therapy. Several studies now suggest that it may be best to start therapy at the time of diagnosis in order to preserve beneficial compensatory mechanisms and possibly provide functional

benefits even in the early stage of the disease. Levodopa remains the most effective symptomatic therapy for PD, and some recommend starting it immediately using relatively low doses, but many others prefer to delay levodopa treatment particularly in younger patients in order to reduce the risk of motor complications. Another approach is to begin with an MAO-B inhibitor and/or a dopamine agonist, and reserve levodopa for later stages when these drugs can no longer provide satisfactory control. In making this decision, the age, degree of disability, and side effect profile of the drug must all be considered. In patients with more severe disability, the elderly, those with cognitive impairment, or where the diagnosis is uncertain, most physicians would initiate therapy with levodopa. Regardless of initial choice, it is important not to deny patients levodopa when they cannot be adequately controlled with alternative medications.

If motor complications develop, they can initially be treated by manipulating the frequency and dose of levodopa, or by combining lower doses of levodopa with a dopamine agonist, a COMT inhibitor, or an MAO-B inhibitor. Amantadine is the only drug that has been demonstrated to treat dyskinesia without worsening parkinsonism, but benefits may be short-lasting and there are important side effects. In severe cases, it is usually necessary to consider a surgical therapy such as DBS if the patient is a suitable candidate, but as described above these procedures have their own set of complications. There are ongoing efforts aimed at developing a long-acting oral or transdermal formulation of levodopa that mirrors the pharmacokinetic properties of a levodopa infusion. Such a formulation might provide all of the benefits of levodopa without motor complications and avoid the need for polypharmacy and surgical intervention.

A decision tree that considers the various treatment options and decision points for the management of PD is provided in Figure 372-7.

HYPERKINETIC MOVEMENT DISORDERS

Hyperkinetic movement disorders are characterized by involuntary movements that may occur in isolation or in combination (Table 372-6). The major hyperkinetic movement disorders and the diseases with which they are associated are considered in this section.

TREMOR

Clinical Features: Tremor consists of alternating contractions of agonist and antagonist muscles in an oscillating, rhythmic manner. It can be most prominent at rest (rest tremor), on assuming a posture (postural tremor), or upon actively reaching for a target (kinetic tremor). Tremor is also assessed based on distribution, frequency, and related neurological dysfunction.

PD is characterized by a resting tremor, essential tremor (ET) by a postural tremor, and cerebellar disease by an intention or kinetic tremor. Normal individuals can have a physiological tremor which typically manifests as a mild, high frequency, postural or action tremor which is usually of no clinical consequence and often is only appreciated with an accelerometer. An enhanced physiological tremor (EPT) can be seen in up to 10% of the population, often in association with anxiety, fatigue, underlying metabolic disturbance (e.g. hyperthyroidism, electrolyte abnormalities), drugs (e.g. valproate, lithium) or toxins (e.g. alcohol). Treatment is initially directed to the control of any underlying disorder, and if necessary, can often be improved with a β-blocker.

ET is the commonest movement disorder, affecting approximately 5-10,000,000 persons in the United States. It can present in childhood, but dramatically increases in prevalence over the age of 70 years. ET is characterized by a high frequency tremor (up to 11Hz) that predominantly affects the upper extremities. The tremor is most often manifest as a postural or kinetic tremor. It is typically bilateral and symmetrical, but may begin on one side and remain asymmetric. Patients with severe ET can have an intention tremor with overshoot and slowness of movement. Tremor involves the head in ~30% of cases, voice in ~20%, tongue in ~20%, face/jaw in ~10% and lower limbs in ~10%. The tremor is characteristically improved by alcohol and worsened by stress. Subtle impairment of coordination or tandem walking may be present. Disturbances of hearing, cognition and even olfaction have been described, but usually the neurological examination is normal aside from tremor. The major differential is a dystonic tremor (see below) or PD. PD can usually be differentiated from ET based on the presence of bradykinesia, rigidity, micrographia and other parkinsonian features. However, the examiner should be aware that PD patients may have a postural tremor and ET patients may develop a rest tremor. These typically begin after a latency of a few seconds (emergent tremor). The examiner must take care to differentiate the effect of tremor on measurement of tone in ET from the cog-wheel rigidity found in PD.

Etiology and Pathophysiology: The etiology and pathophysiology of ET are not known. Approximately 50% of cases have a positive family history with an autosomal dominant pattern of inheritance. Linkage studies have detected loci at chromosome 3q13 (ETM-1), 2p22-25 (ETM-2) and 6p23 (ETM-3). Recent genome-wide studies demonstrate an association with the LINGO1 gene, particularly in patients with young onset ET, and it is

likely that there are many other undiscovered loci. Candidate genes include the dopamine D3 receptor and proteins that map to the cerebellum. The cerebellum and inferior olives have been implicated as possible sites of a "tremor pacemaker" based on the presence of cerebellar signs and increased metabolic activity and blood flow in these regions in some patients. Recent pathological studies have described cerebellar pathology with a loss of Purkinje cells and axonal torpedoes. However, the precise pathological correlate of ET remains to be defined.

Treatment: Many cases are mild and require no treatment other than reassurance. Occasionally, tremor can be severe and interfere with eating, writing, and activities of daily living. This is more likely to occur as the patient ages and is often associated with a reduction in tremor frequency. Beta blockers or primidone are the standard drug therapies for ET and help in about 50% of cases. Propranolol (20-80 mg daily given in divided doses) is usually effective at relatively low doses, but higher doses may be effective in some patients. The drug is contraindicated in patients with bradycardia or asthma. Hand tremor tends to be most improved, while head tremor is often refractory. Primidone can be helpful, but should be started at low doses (12.5 mg) and gradually increased (125-250 tid) to avoid sedation. Benefits have been reported with gabapentin and topiramate. Botulinum toxin injections may be helpful for limb or voice tremor, but treatment can be associated with secondary muscle weakness. Surgical therapies targeting the VIM nucleus of the thalamus can be very effective for severe and drug-resistant cases.

DYSTONIA

Clinical Features: Dystonia is a disorder characterized by sustained or repetitive involuntary muscle contractions frequently associated with twisting or repetitive

movements and abnormal postures. Dystonia can range from minor contractions in an individual muscle group to severe and disabling involvement of multiple muscle groups. The frequency is estimated at 300,000 cases in the United States, but is likely much higher as many cases may not be recognized. Dystonia is often brought out by voluntary movements (action dystonia), and can become sustained and extend to involve other body regions. It can be aggravated by stress and fatigue, and attenuated by relaxation and sensory tricks such as touching the affected body part (geste antagoniste). Dystonia can be classified based on age of onset (childhood vs adult), distribution (focal, multifocal, segmental, or generalized), or etiology (primary or secondary).

Primary Dystonias: Several gene mutations are associated with dystonia. Idiopathic Torsion Dystonia (ITD) or Oppenheim's dystonia is predominantly a childhood onset form of dystonia with an autosomal dominant pattern of inheritance that primarily affects Ashkenazi Jewish families. The majority of patients have an age of onset younger than 26 years (mean 14 years). In young onset patients, dystonia typically begins in the foot or the arm and in 60-70% progresses to involve other limbs as well as the head and neck. In severe cases, patients can suffer disabling postural deformities that compromise mobility. Severity can vary within a family, with some affected relatives having severe disability and others a mild dystonia that may not even be appreciated. Most childhood onset cases are linked to a mutation in the DYT1 gene located on chromosome 9q34 resulting in a trinucleotide GAG deletion with loss of one of a pair of glutamic acid residues in the protein Torsin A. DYT1 mutations are found in 90% of Ashkenazi Jewish patients with ITD, and probably relate to a founder effect that occurred about 350 years ago. There is variable penetrance, with only about 30% of gene carriers expressing a clinical

phenotype. Why some gene carriers express dystonia and others do not is not known. The function of Torsin A is unknown, but it is a member of the AAA^+ (ATPase) family that resemble heat shock proteins and may be related to protein regulation. The precise pathology responsible for dystonia is not known.

Dopa Responsive Dystonia (DRD) or the Segawa variant (DYT5) is a dominantly inherited form of childhood onset dystonia due to a mutation in the gene that encodes for GTP cyclohydrolase-I, the rate-limiting enzyme for the synthesis of tetrahydrobiopterin. This mutation leads to a defect in the biochemical synthesis of tyrosine hydroxylase, the rate limiting enzyme in the formation of dopamine. DRD typically presents in early childhood (1-12 years), and is characterized by foot dystonia that interferes with walking. Patients often experience diurnal fluctuations with worsening of gait as the day progresses and improvement with sleep. DRD is typified by an excellent and sustained response to small doses of levodopa. Some patients may present with parkinsonian features, but can be differentiated from juvenile PD by normal striatal fluorodopa uptake on positron emission tomography and the absence of levodopa-induced dyskinesias. DRD may occasionally be confused with cerebral palsy because patients appear to have spasticity, increased reflexes and a Babinski responses (which likely reflect a dystonic contraction rather than an upper motor neuron lesion). Any patient suspected of having a childhood onset dystonia should receive a trial of levodopa to exclude this condition.

Mutations in the *THAP1* gene (DYT6) on chromosome 8p21q22 have been identified in Amish families and are the cause of as many as 25% of cases of non DYT1 young-onset primary torsion dystonia. Patients are more likely to have dystonia beginning in the brachial and cervical muscles, which later can become generalized and

associated with speech impairment. Myoclonic-dystonia (DYT11) results from a mutation in the epsilon-sarcoglycan gene on chromosome 7q21. It typically manifests as a combination of dystonia and myoclonic jerks, frequently accompanied by psychiatric disturbances.

Focal Dystonias: These are the most common forms of dystonia. They typically present in the 4^{th} to 6^{th} decades and affect women more than men. The major types are: (1) *blepharospasm* – dystonic contractions of the eyelids with increased blinking that can interfere with reading, watching TV and driving. This can sometimes be so severe as to cause functional blindness. (2) *Oromandibular dystonia* (OMD) –contractions of muscles of the lower face, lips, tongue and jaw (opening or closing). Meige syndrome is a combination of OMD and blepharospasm that predominantly affects women over the age of 60 years. (3) *Spasmodic dysphonia* - dystonic contractions of the vocal cords during phonation causing impaired speech. Most cases affect the adductor muscles and cause speech to have a choking or strained quality. Less commonly the abductors are affected leading to speech with a breathy or whispering quality. (4) *Cervical dystonia* – dystonic contractions of neck muscles causing the head to deviate to one side (*torticollis*), in a forward direction (*anterocollis*) or in a backward direction *(retrocollis).* Muscle contractions can be painful, and associated with a secondary cervical radiculopathy. (5) *Limb dystonias* – These can be present in either arms or legs and are often brought out by task-specific activities such as handwriting (writer's cramp), playing a musical instrument (musician's cramp) or putting (the yips). Focal dystonias can extend to involve other body regions (about 30% of cases), and are frequently misdiagnosed as psychiatric or orthopedic in origin. Their cause is not known, but genetic factors, autoimmunity, and

trauma have been suggested. Focal dystonias are often associated with a high frequency tremor that resembles ET. Dystonic tremor can usually be distinguished from ET because it tends to occur in conjunction with the dystonic contraction and disappears when the dystonia is relieved.

Secondary dystonias: These develop as a consequence of drugs or other neurologic disorders. Drug-induced dystonia is most commonly seen with neuroleptic drugs or after chronic levodopa treatment in PD patients. Secondary dystonia can also be observed following discrete lesions in the striatum, pallidum, thalamus, cortex, and brainstem due to infarction, anoxia, trauma, tumor, infection, or toxins such as manganese, or carbon monoxide. In these cases, dystonia often assumes a segmental distribution. More rarely, dystonia can develop following peripheral nerve injury and be associated with features of chronic regional pain syndrome.

Dystonia Plus Syndromes: Dystonia may occur as a part of neurodegenerative conditions such as HD, PD, Wilson's disease, CBGD, PSP, the Lubag form of dystonia-parkinsonism (DYT3), and mitochondrial encephalopathies. In contrast to the primary dystonias, dystonia is usually not the dominant neurological feature in these conditions.

Pathophysiology of Dystonia: The pathophysiologic basis of dystonia is not known. The phenomenon is characterized by co-contracting synchronous bursts of agonist and antagonist muscle groups. This is associated with a loss of inhibition at multiple levels of the nervous system as well as increased cortical excitability and reorganization. Attention has focused on the basal ganglia as the site of origin of at least some types of dystonia as there are alterations in blood flow and metabolism in basal ganglia structures. Further, ablation or stimulation of the globus pallidus can both induce and ameliorate dystonia.

The dopamine system has also been implicated as dopaminergic therapies can both induce and treat some forms of dystonia.

Treatment: Treatment of dystonia is for the most part symptomatic except in rare cases where treatment of a primary underlying condition is available. Wilson's disease should be ruled out in young patients with dystonia. Levodopa should be tried in all cases of childhood onset dystonia to rule out DRD. High dose anticholinergics (e.g., trihexyphenidyl 20-120 mg/d) may be beneficial in children, but adults can rarely tolerate high doses because of cognitive impairment with hallucinations. Oral baclofen (20-120 mg) may be helpful, but benefits if present are usually modest and side effects of sedation, weakness, and memory loss can be problematic. Intrathecal infusion of baclofen is more likely to be helpful particularly with leg and trunk dystonia, but benefits are frequently not sustained and complications can be serious and include infection, seizures and coma. Tetrabenzine (12.5-200 mg/d) may be helpful in some patients, but use may be limited by sedation and the development of parkinsonism. Neuroleptics can improve as well as induce dystonia, but are typically not recommended because of their potential to induce extrapyramidal side effects including tardive dystonia. Clonazepam and diazepam are rarely effective.

Botulinum toxin has become the preferred treatment for patients with focal dystonia, particularly where involvement is limited to small muscle groups such as in blepharospasm, torticollis, and spasmodic dysphonia. Botulinum toxin acts by blocking the release of acetylcholine at the neuromuscular junction leading to muscle weakness and reduced dystonia, but excessive weakness may ensue and can be troublesome particularly if it involves neck and swallowing muscles. Two serotypes of botulinum

toxin are available (A and B). Both are effective, and it is not clear that there are advantages of one over the other. No systemic side effects are encountered with the doses typically employed, but benefits are transient and repeat injections are required at 2 to 5 month intervals. Some patients fail to respond after having experienced an initial benefit. This has been attributed to antibody formation, but improper muscle selection, injection technique, and inadequate dose should be excluded.

Surgical therapy is an alternative for patients with severe dystonia who are not responsive to other treatments. Peripheral procedures such as rhizotomy and myotomy were used in the past to treat cervical dystonia, but are now rarely employed. DBS of the pallidum can provide dramatic benefits for patients with primary DYT1 dystonia. This represents a major therapeutic advance as previously there was no consistently effective therapy especially for these patients who had severe disability. Benefits tend to be obtained with a lower frequency of stimulation and often occur after a relatively long latency (weeks) in comparison to PD. Better results are typically obtained in younger patients. Recent studies suggest that DBS may also be valuable for patients with focal and secondary dystonias, although results are less consistent. Supportive treatments such as physical therapy and education are important and should be a part of the treatment regimen.

Physicians should be aware of dystonic storm, a rare but potentially fatal condition that can occurs in response to a stress situation such as surgery in patients with pre-existing dystonia. It consists of the acute onset of generalized and persistent dystonic contractions that can involve the vocal cords or laryngeal muscles leading to airway obstruction. Patients may experience rhabodmyolysis with renal failure. Patients should

be managed in an ICU with protection of airway if required. Treatment can be instituted with one or a combination of anticholinergics, diphenhydramine, baclofen, benzodiazpines, and dopamine agonists/antagonists. Spasms may be difficult to control and anesthesia with muscle paralysis may be required.

CHOREAS

Huntington's Disease (HD): HD is a progressive, fatal, highly penetrant autosomal dominant disorder characterized by motor, behavioral, and cognitive dysfunction. The disease is named for George Huntington, a family physician who described cases on Long Island, NY in the 19th century. Onset is typically between the ages of 25 and 45 years (range 3 to 70 years) with a prevalence of 2-8 cases per 100,000 and an average age at death of 60 years. It is prevalent in Europe, North and South America and Australia, but is rare in African blacks and Asians. HD is characterized by rapid, non-patterned, semi-purposeful, involuntary choreiform movements. In the early stages the chorea tends to be focal or segmental, but progresses over time to involve multiple body regions. Dysarthria, gait disturbance, and oculomotor abnormalities are common features. With advancing disease, there may be a reduction in chorea and emergence of dystonia, rigidity, bradykinesia, myoclonus and spasticity. Functional decline is often predicted by progressive weight loss despite adequate calorie intake. In younger patients (about 10% of cases) HD can present as an akinetic-rigid or parkinsonian syndrome (Westphall variant). HD patients eventually develop behavioral and cognitive disturbances and the majority progress to dementia. Depression with suicidal tendencies, aggressive behavior, and psychosis can be prominent features. HD patients may also develop non-insulin-dependent diabetes mellitus and neuroendocrine abnormalities e.g. hypothalamic

dysfunction. A clinical diagnosis of HD can be strongly suspected in cases of chorea with a positive family history. The disease predominantly strikes the striatum. Progressive atrophy of the caudate nuclei, which form the lateral margins of the lateral ventricles, can be visualized by MRI (Fig. 372-8 [Fig. 367-1 in HPIM17]). More diffuse cortical atrophy is seen in the middle and late stages of the disease. Supportive studies include reduced metabolic activity in the caudate nucleus and putamen. Genetic testing can be used to confirm the diagnosis and to detect at risk individuals in the family, but this must be performed with caution and in conjunction with trained counselors, as positive results can worsen depression and generate suicidal reactions. The neuropathology of HD consists of prominent neuronal loss and gliosis in the caudate nucleus and putamen (Fig. 372-7); similar changes are also widespread in the cerebral cortex. Intraneuronal inclusions containing aggregates of ubiquitin and the mutant protein huntingtin are found in nuclei of affected neurons.

Etiology: HD is caused by an increase in the number of polyglutamine (CAG) repeats (>40) in the coding sequence of the huntingtin gene located on the short arm of chromosome 4. The larger the number of repeats, the earlier the disease is manifest. Acceleration of the process tends to occur, particularly in males, with subsequent generations having larger numbers of repeats and earlier age of disease onset, a phenomenon referred to as anticipation. The gene encodes the highly conserved cytoplasmic protein huntingtin, which is widely distributed in neurons throughout the CNS, but whose function is not known. Models of HD with striatal pathology can be induced by excitotoxic agents such as kianic acid and 3-nitroproprionic acid which promote calcium entry into the cell and cytotoxicity. Mitochondrial dysfunction has been

demonstrated in the striatum and skeletal muscle of symptomatic and pre-symptomatic individuals. Fragments of the mutant huntingtin protein can be toxic, possibly by translocating into the nucleus and interfering with transcriptional upregulation of regulatory proteins. Neuronal inclusions found in affected regions in HD may represent a protective mechanism aimed at segregating and facilitating the clearance of these toxic proteins.

Treatment: Treatment involves a multidisciplinary approach with medical, neuropsychiatric, social, and genetic counseling for patients and their families. Dopamine blocking agents may control the chorea. Tetrabenazine has recently been approved for the treatment of chorea in the United States, but may cause secondary parkinsonism. Neuroleptics are generally not recommended because of their potential to induce other more troubling movement disorders, and because HD chorea tends to be self-limited and is usually not disabling. Depression and anxiety can be greater problems, and patients should be treated with appropriate antidepressant and anti-anxiety drugs and monitored for mania and suicidal ideations. Psychosis can be treated with atypical neuroleptics such as clozapine (50-600 mg/d), quetiapine (50-600 mg/d), and risperidone (2-8 mg/d). There is no adequate treatment for the cognitive or motor decline. A neuroprotective therapy that slows or stops disease progression is the major unmet medical need in HD. Pro-mitochondrial agents such as ubiquinone, and creatine are being tested as possible disease-modifying therapies. Antiglutamate agents, caspase inhibitors, inhibitors of protein aggregation, neurotrophic factors and transplantation of fetal striatal cells are areas of active research, but none has as yet been demonstrated to have a disease-modifying effect.

Huntington's disease-like 1 (HDL1), Huntington's disease-like 2 (HDL2)

HDL1 is a rare inherited disorder due to mutations of the protein located at 20p12. Patients exhibit onset of personality change in the 3rd or 4th decade, followed by chorea, rigidity, myoclonus, ataxia and epilepsy. HDL2 is an autosomal-dominantly inherited disorder manifesting in the 3rd or 4th decade with a variety of movement disorders, including chorea, dystonia or parkinsonism and dementia. Most patients are of African descent. Acanthocytosis can sometimes be seen in these patients and they must be differentiated from neuroacanthocytosis. HDL2 is caused by an abnormally expanded CTG/CAG trinucleotide repeat expansion in the *junctophilin-3* (*JPH3*) gene on chromosome 16q24.3. The pathology of HDL2 also demonstrates intranuclear inclusions immunoreactive for ubiquitin and expanded polyglutamine repeats.

Other Choreas: Chorea can be seen in a number of disorders. Sydenham's chorea (originally called St Vitus' dance) is more common in females and is typically seen in childhood (5-15 years). It often develops in association with prior exposure to group A streptococcal infection, and is thought to be autoimmune in nature. With the reduction in the incidence of rheumatic fever the incidence of Sydenham's chorea has fallen, but it can still be seen in developing countries. It is characterized by the acute onset of choreiform movements, behavioral disturbances, and occasionally other motor dysfunctions. Chorea generally responds to dopamine blocking agents, valproic acid, and carbamazepine, but is self-limited and treatment is generally restricted to those with severe chorea. Chorea may recur in later life, particularly in association with pregnancy (chorea gravidarum) or treatment with sex hormones.

Chorea-acanthocytosis (neuroacanthocytosis) is a progressive and typically fatal autosomal recessive disorder that is characterized by chorea coupled with red cell abnormalities on peripheral blood smear (acanthocytes). The chorea can be severe and associated with self-mutilating behavior, dystonia, tics, seizures, and a polyneuropathy. Mutations in the *VPS13A* gene on chromosome 9q21 encoding chorein have been described. A phenotypically similar X-linked form of the disorder has been described in older individuals who have reactivity with Kell blood group antigens (McLeod Syndrome). A benign hereditary chorea of childhood (BHC1) due to mutations in the gene for thyroid transcription factor 1 and a late onset benign senile chorea (BHC2) have also been described. It is important to ensure that patients with these types of choreas do not have HD.

A range of neurodegenerative diseases with brain iron accumulation (NBIA) manifesting with chorea and dystonia have been described including autosomal dominant neuroferritinopathy, autosomal recessive pantothenate-kinase associated neurodegeneration (PKAN; Hallevortan-Spatz disease) and aceruloplasminemia. These disorders have excess iron accumulation on MRI and a characteristic 'eye of the tiger' appearance in the globus pallidus due to iron accumulation.

Chorea may also occur in association with vascular diseases, hypo- and hyperglycemia, and a variety of infections and degenerative disorders. Systemic lupus erythematosis is the most common systemic disorder that causes chorea; the chorea can last for days to years. Choreas can also be seen with hyperthyroidism, autoimmune disorders including

Sjogren's syndrome, infectious disorders including HIV disease, metabolic alterations, polycythemia rubra vera, following open heart surgery in the pediatric population, and in association with many medications (especially anticonvulsants, cocaine, CNS stimulants, estrogens, lithium). Chorea can also be seen in paraneoplastic syndromes associated with anti-CRMP-5 or anti-Hu antibodies.

Paroxysmal dyskinesias are a group of rare disorders characterized by episodic, brief involuntary movements that can include chorea, dystonia, and ballismus. Paroxysmal kinesigenic dyskinesia (PKD) is a familial childhood onset disorder in which chorea or chorea-dystonia is precipitated by sudden movement or running. Attacks may affect one side of the body, last seconds to minutes at a time, and recur several times a day. Prognosis is usually good with spontaneous remission in later life. Low dose anti-convulsant therapy (e.g. carbamazepine) is usually effective if required. Paroxysmal non-kinesigenic dyskinesia (PNKD) involves attacks of dyskinesia precipitated by alcohol, caffeine, stress or fatigue. Like PKD, it is familial and childhood in onset and the episodes are often choreic or dystonic, but have longer duration (minutes to hours) and are less frequent (1-3/day).

Treatment: Diagnosis and treatment of the underlying condition, where possible, is the first priority. Tetrabenazine, neuroleptics, dopamine blocking agents, propranolol, clonazepam, and baclofen may be helpful. Treatment is not indicated if the condition is mild and self-limited. Most patients with PKND do not benefit from anticonvulsant drugs but some may respond to clonazepam.

Hemiballismus: Hemiballismus is a violent form of chorea comprised of wild, flinging, large amplitude movements on one side of the body. Proximal limb muscles tend to be predominantly affected. The movements may be so severe as to cause exhaustion, dehydration, local injury, and in extreme cases, death. The most common cause is a partial lesion (infarct or hemorrhage) in the subthalamic nucleus (STN), but rare cases can also be seen with lesions in the putamen. Fortunately, hemiballismus is usually self-limiting and tends to resolve spontaneously after weeks or months. Dopamine blocking drugs can be helpful, but can themselves lead to movement disorders. In extreme cases, pallidotomy can be very effective. Interestingly, surgically induced lesions or DBS of the STN in PD are usually not associated with hemiballismus.

TICS

Tourette syndrome (TS): TS is a neurobehavioral disorder named after the French neurologist Georges Gilles de la Tourette. It predominantly affects males, and prevalence is estimated to be 0.03-1.6%, but it is likely that many mild cases do not come to medical attention. TS is characterized by multiple motor tics often accompanied by vocalizations (phonic tics). A *tic* is a brief, rapid, recurrent, and seemingly purposeless stereotyped motor contraction. Motor tics can be "simple" with movement only affecting an individual muscle group (e.g. blinking, twitching of the nose, jerking of the neck), or "complex" with coordinated involvement of multiple muscle groups (e.g. jumping, sniffing, head banging, and echopraxia (mimicking movements)). Vocal tics can also be simple (e.g. grunting) or complex (e.g. echolalia (repeating other peoples words), palilalia (repeating your own words), and coprolalia (expression of obscene words)). Patients may also experience sensory tics, comprised of unpleasant focal sensations in the face, head,

or neck. Patients characteristically can voluntarily suppress tics for short periods of time, but then experience an irresistible urge to express them. Tics vary in intensity and may be absent for days or weeks only to recur, occasionally in a different pattern. Tics tend to present between ages 2 to 15 years (mean 7 years) and often lessen or even disappear in adulthood. Associated behavioral disturbances include anxiety, depression, ADHD and obsessive compulsive disorder (OCD). Patients may experience personality disorders, self-destructive behaviors, difficulties in school, and impaired interpersonal relationships. Tics may present in adulthood and can be seen in association with a variety of other disorders including PD, HD, trauma, dystonia, drugs (eg levodopa, neuroleptics), and toxins.

Etiology and Pathophysiology: TS is thought to be a genetic disorder, but no specific gene mutation has been identified. Current evidence supports a complex inheritance pattern with one or more major genes, multiple loci, low penetrance, and environmental influences. The risk of a family with one affected child having a second is about 25%. The pathophysiology of TS is not known, but alterations in dopamine neurotransmission, opioids, and second messenger systems have been proposed. Some cases of TS may be the consequence of an autoimmune response to β-hemolytic streptococcal infection, (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS)) although this remains controversial.

Treatment: Patients with mild disease often only require education and counseling (for themselves and family members). Drug treatment is indicated when the tics are disabling and interfere with quality of life. Therapy is generally initiated with the alpha-agonist clonidine, starting at low doses and gradually increasing the dose and frequency until

satisfactory control is achieved. Guanfacine (0.5 to 2 mg/d) is an alpha-agonist that is preferred by many clinicians because it only requires once a day dosing. If these agents are not effective, anti-psychotics can be employed. Atypical neuroleptics (risperidone, olanzapine, ziprasidone) are preferred as they are thought to be associated with a reduced risk of extrapyramidal side effects. If they are not effective, low doses of classical neuroleptics such as haloperidol, fluphenazine, or pimozide can be tried. Botulinum toxin injections can be effective in controlling focal tics that involve small muscle groups. Behavioral features, and particularly anxiety and compulsions, can be a disabling feature of TS and should be treated. The potential value of DBS targeting the anterior portion of the internal capsule is currently being explored.

MYOCLONUS

Myoclonus is a brief, rapid (<100msec) shock-like, jerky movement consisting of single or repetitive muscle discharges. Myoclonic jerks can be focal, multifocal, segmental or generalized and can occur spontaneously, in association with voluntary movement (action myoclonus) or in response to an external stimulus (reflex or startle myoclonus). Negative myoclonus consists of a twitch due to a brief loss of muscle activity (e.g. asterixis in hepatic failure). Myoclonic jerks differ from tics in that they interfere with normal movement and are not suppressible. They can be seen in association with pathology in cortical, subcortical, or spinal cord regions, and associated with hypoxic damage (especially following cardiac arrest), encephalopathy, and neurodegeneration. Reversible myoclonus can be seen with metabolic disturbances (renal failure, electrolyte imbalance, hypocalcemia), toxins, and many medications. Essential myoclonus is a relatively benign familial condition characterized by multifocal lightning-like movements. Myoclonic jerks

can be disabling when they interfere with normal movement. They can also be innocent and are commonly observed in normal people when waking up or falling asleep (hypnogogic jerks).

Treatment: Treatment primarily consists of treating the underlying condition or removing an offending agent. Pharmacologic therapy involves one or a combination of gabaergic agents such as valproic acid (800-3000 mg/day), piracetam (8-20g/day), clonazepam (2-15mg/day), or primidone (500-1000 mg/day). Recent studies suggest that levetiracetam may be particularly effective.

DRUG-INDUCED MOVEMENT DISORDERS

This important group of movement disorders is primarily associated with drugs that block dopamine receptors (neuroleptics) or central dopaminergic transmission. These drugs are primarily used in psychiatry, but it is important to appreciate that drugs used in the treatment of nausea or vomiting (e.g. compazine) or gastroesophageal disorders (e.g. metoclopromide) are neuroleptic agents. Hyperkinetic movement disorders secondary to neuroleptic drugs can be divided into those which present acutely, sub-acutely or after prolonged exposure (tardive syndromes). Dopamine blocking drugs can also be associated with a reversible parkinsonian syndrome for which anticholinergics are often concomitantly prescribed, but there is concern that this may increase the risk of developing a tardive syndrome.

Acute: Dystonia is the most common acute hyperkinetic drug reaction. It is typically generalized in children and focal in adults (e.g., blepharospasm, torticollis, or oromandibular dystonia). The reaction can develop within minutes of exposure, and can

be successfully treated in most cases with parenteral administration of anticholinergics (benztropine or diphenhydramine) or benzodiazepines (lorazepam or diazepam). Choreas, stereotypic behaviors, and tics may also be seen, particularly following acute exposure to CNS stimulants such as methylphenidate, cocaine, or amphetamines.

Subacute: Akathisia is the commonest reaction in this category. It consists of motor restlessness with a need to move that is alleviated by movement. Therapy consists of removing the offending agent. When this is not possible, symptoms may be ameliorated with benzodiazepines, anticholinergics, beta blockers, or dopamine agonists.

Tardive syndromes: These disorders develop months to years after initiation of neuroleptic treatment. Tardive dyskinesia (TD) is the commonest and is typically comprised of choreiform movements involving the mouth, lips, and tongue. In severe cases the trunk, limbs, and respiratory muscles may also be affected. In approximately one-third of patients, TD remits within 3 months of stopping the drug, and most patients gradually improve over the course of several years. In contrast, abnormal movements may develop after stopping the offending agent. The movements are often mild and more upsetting to the family than to the patient, but they can be severe and disabling particularly in the context of an underlying psychiatric disorder. Atypical antipsychotics (e.g. clozapine, risperidone, olanzepine, quetiapine, ziprasidone, and aripiprazole) are associated with a significantly lower risk of TD in comparison to traditional antipsychotics. Younger patients have a lower risk of developing neuroleptic-induced TD, while the elderly, females, and those with underlying organic cerebral dysfunction have been reported to be at greater risk. In addition, chronic use is associated with increased risk and specifically the FDA has warned that use of metoclopramide for more

than 12 weeks increases the risk of TD. Since TD can be permanent and resistant to treatment, antipsychotics should be used judiciously, atypical neuroleptics should be the preferred agent whenever possible, and the need for their continued use should be regularly monitored.

Treatment primarily consists of stopping the offending agent. If the patient is receiving a traditional antipsychotic and withdrawal is not possible, replacement with an atypical antipsychotic should be tried. Abrupt cessation of a neuroleptic should be avoided as acute withdrawal can induce worsening. TD can persist after withdrawal of anti-psychotics and can be difficult to treat. Benefits may be achieved with valproic acid, anticholinergics or botulinum toxin injections. In refractory cases, catecholamine depletors such as tetrabenazine may be helpful. Tetrabenazine can be associated with dose-dependent sedation and orthostatic hypotension. Other approaches include baclofen (40 to 80 mg/day), clonazepam (1 to 8 mg/day), or valproic acid (750 to 3,000 mg/day).

Chronic neuroleptic exposure can also be associated with tardive dystonia with preferential involvement of axial muscles and characteristic rocking movements of the trunk and pelvis. Tardive dystonia frequently persists despite stopping medication and patients are often refractory to medical therapy. Valproic acid, anticholinergics and botulinum toxin may occasionally be beneficial. Tardive akathisia, tardive Tourette, and tardive tremor syndromes are rare, but may also occur after chronic neuroleptic exposure.

Neuroleptic medications can also be associated with a neuroleptic malignant syndrome (NMS). NMS is characterized by muscle rigidity, elevated temperature, altered mental status, hyperthermia, tachycardia, labile blood pressure renal failure and markedly elevated creatine kinase levels. Symptoms typically evolve within days or weeks after

initiating the drug. NMS can also be precipitated by the abrupt withdrawal of antiparkinsonian medications in PD patients. Treatment involves immediate cessation of the offending antipsychotic drug, and the introduction of a dopaminergic agent (e.g. a dopamine agonist or levodopa), dantrolene, or a benzodiazepine. Treatment may need to be undertaken in an intensive care setting and includes supportive measures such as control of body temperature (antipyretics and cooling blankets), hydration, electrolyte replacement, and control of renal function and blood pressure.

Drugs that have serotonin-like activity (tryptophan, MDMA or "ecstasy", meperidine) or that block serotonin reuptake can induce a rare, but potentially fatal, serotonin syndrome that is characterized by confusion, hyperthermia, tachycardia and coma as wells as rigidity, ataxia, and tremor. Myoclonus is often a prominent feature, in contrast to NMS which it resembles. Patients can be managed with propanolol, diazepam, diphenhydramine, chlorpromazine, or cyproheptadine as well as supportive measures.

A variety of drugs can also be associated with parkinsonism (see above) and hyperkinetic movement disorders. Some examples include phenytoin (chorea, dystonia, tremor, myoclonus), carbamazepine (tics and dystonia), tricyclic andtidepressants (dyskinesias, tremor, myoclonus), fluoxetine (myoclonus, chorea, dystonia), oral contraceptives (dyskinesia). beta adrenergics (tremor), buspirone (akathisia, dyskinesias, myoclonus), and digoxin, cimetidine, diazoxide, lithium, methadone, and fentanyl (dyskinesias).

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is a neurological disorder that affects approximately 10% of the adult population (it is rare in Asians) and can cause significant morbidity in some. It was first described in the 17th century by an English physician (Thomas Willis), but has only recently been recognised as being a bona fide movement disorder. The four core symptoms required for diagnosis are: an urge to move the legs, usually caused or accompanied by an unpleasant sensation in the legs; symptoms begin or worsen with rest; partial or complete relief by movement; worsening during the evening or night.

Symptoms most commonly begin in the legs, but can spread to or even begin in the upper limbs. The unpleasant sensation is often described as a creepy-crawly feeling, parathesia, or burning. In about 80% of patients, RLS is associated with periodic leg movements (PLMs) during sleep and occasionally while awake. These involuntary movements are usually brief, lasting no more than a few seconds, and recur every 5–90 seconds. The restlessness and PLMs are a major cause of sleep disturbance in patients, leading to poor quality sleep and daytime sleepiness.

RLS is a heterogeneous condition. Primary RLS is genetic, and several loci have been found with an autosomal dominant pattern of inheritance, although penetrance may be variable. The mean age of onset in genetic forms is 27 years although pediatric cases are recognized. The severity of symptoms is variable. Secondary RLS may be associated with pregnancy or a range of underlying disorders including anemia, ferritin deficiency, renal failure and peripheral neuropathy. The pathogenesis probably involves disordered dopamine function that may be peripheral or central, in association with an abnormality of iron metabolism. Diagnosis is made on clinical grounds but can be supported by polysomnography and the demonstration of PLMs. The neurological examination is

normal. Secondary RLS should be excluded and ferritin levels, glucose and renal function should be measured.

Most RLS sufferers have mild symptoms that do not require specific treatment. General measures to improve sleep hygiene and quality should be attempted first. If symptoms remain intrusive, low doses of dopamine agonists e.g. pramipexole (0.25-0,5 mg), ropinirole (1-2 mg) are given 1-2 hours before bedtime. Levodopa can be effective but is frequently associated with augmentation (spread and worsening of restlessness and its appearance earlier in the day) or rebound (reappearance sometimes with worsening of symptoms at a time compatible with the drug's short half-life). Other drugs that can be effective include anticonvulsants, analgesics, and even opiates. Management of secondary RLS should be directed to correcting the underlying disorder; for example, iron replacement for anemia. Iron infusion may also be helpful for severe primary RLS but requires expert supervision.

DISORDERS THAT PRESENT WITH PARKINSONISM AND HYPERKINETIC MOVEMENTS

Wilson's Disease: Wilson's disease (WD) is an autosomal recessive inherited disorder of copper metabolism that may manifest with neurologic, psychiatric and liver disorders, alone or in combination. It is caused by mutations in the gene encoding a P-type ATPase. The disease was first comprehensively described by the English neurologist Kinnear Wilson at the beginning of the 20th century, although at around the same time the German physicians Kayser and Fleischer separately noted the characteristic association of corneal pigmentation with hepatic and neurological features. WD has a worldwide prevalence of

approximately 1 in 30,000, with a gene carrier frequency of 1 in 90. About half of WD patients (especially younger patients) manifest with liver abnormalities. The remainder present with neurological disease (with or without underlying liver abnormailities), and a small proportion have hematologic or psychiatric problems at disease onset.

Neurologic onset usually manifests in the second decade with tremor and rigidity. The tremor is usually in the upper limbs, bilateral, and asymmetrical. Tremor can be on intention or occasionally resting, and in advanced disease can take on a wing-beating characteristic. Other features include parkinsonism with bradykinesia, dystonia (particularly facial grimacing), dysarthria, and dysphagia. Over half of those with neurological features have a history of psychiatric disturbances including depression, mood swings and overt psychosis. Kayser-Fleischer (KF) rings are seen in 80% of those with hepatic presentations and virtually all with neurological features. KF rings represent the deposition of copper in Descemet's membrane around the cornea. They consist of a characteristic grayish rim or circle at the limbus of the cornea and are best detected by slit lamp examination. Neuropathological examination is characterized by neurodegeneration and astrogliosis, particularly in the basal ganglia.

WD should always be considered in the differential diagnosis of a movement disorder in a child. Low levels of blood copper and ceruloplasmin and high levels of urinary copper may be present, but normal levels do not exclude the diagnosis. CT brain scan usually reveals generalized atrophy in established cases and ~50% have hypointensity in the caudate head, globus pallidum, substantia nigra and red nucleus. MRI shows symmetrical hyperintensity on T2-weighted images in the putamen, caudate and pallidum. However, correlation of imaging changes with clinical features is not good.

It is very rare for WD patients with neurological features not to have KF rings. Nevertheless, liver biopsy with demonstration of high copper levels remains the gold standard for the diagnosis.

In the absence of treatment, the course is progressive and leads to severe neurological dysfunction and early death. Treatment is directed at reducing tissue copper levels and maintenance therapy to prevent re-accumulation. There is no clear consensus on treatment and all patients should be managed in a unit with expertise in WD. Penicillamine is frequently used to increase copper excretion, but it may lead to a worsening of symptoms in the initial stages of therapy. Side effects are common and can to some degree be attenuated by co-administration of pyridoxine. Tetrathiomolybdate blocks the absorption of copper and is used instead of penicillamine in many centers. Trientine and zinc are useful drugs for maintenance therapy. Effective treatment can reverse the neurologic features in most patients, particularly when started early. Some patients stabilize and a few may still progress, especially those with hepatocerebral disease. KF rings tend to decrease after 3-6 months and disappear by 2 years. Adherence to maintenance therapy is a major challenge in long term care.

Other Disorders: Pantothenate kinase (PANK)-associated neurodegeneration, acanthocytosis, and Huntington's disease can also present with parkinsonism associated with involuntary movements.

PSYCHOGENIC DISORDERS

Virtually all movement disorders including tremor, tics, dystonia, myoclonus, chorea, ballism and parkinsonism can be psychogenic in origin. Tremor affecting the upper limbs

is the most common psychogenic movement disorder. Psychogenic movements can result from a somatoform or conversion disorder, malingering (e.g. seeking financial gain), or a factitious disorder (e.g. seeking psychological gain). Psychogenic movement disorders are common (estimated 2-3% of patients in a movement disorder clinic), more frequent in women, disabling for the patient and family, and expensive for society (estimated $20 billion annually). Clinical features suggesting a psychogenic movement disorder include an acute onset and a pattern of abnormal movement that is inconsistent with a known movement disorder. Diagnosis is based on the non-organic quality of the movement, the absence of findings of an organic disease process, and positive features that specifically point to a psychogenic illness such as variability and distractability. For example, the magnitude of a psychogenic tremor is increased with attention and diminishes or even disappears when the patient is distracted by being asked to perform a different task or is unaware that he or she is being observed. Other positive features suggesting a psychogenic problem include a tremor frequency that is variable or that entrains with the frequency of movement in the contralateral limb, and a positive response to placebo medication. Associated features can include non-anatomic sensory findings, give-way weakness and astasia abasia (an odd, gyrating gait; Chap. 24). Comorbid psychiatric problems such as anxiety, depression and emotional trauma may be present, but are not necessary for the diagnosis of a psychogenic movement disorder to be made. Psychogenic movement disorders can occur as an isolated entity, or in association with an underlying organic problem. The diagnosis can often be made based on clinical features alone and unnecessary tests or medications avoided. Underlying psychiatric problems may be present and should be identified and treated, but many patients with psychogenic

movement disorders have no obvious psychiatric pathology. Psychotherapy and hypnosis may be of value for patients with conversion reaction, and cognitive behavioral therapy may be helpful for patients with somatoform disorders. Patients with hypochondriasis, factitious disorders and malingering have a poor prognosis.

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Table 372-1: Clinical Features of Parkinson's Disease

Cardinal features	Other Motor Features	Non-motor features
Bradykinesia	Micrographia	Anosmia
Rest tremor	Masked facies (hypomimia)	Sensory disturbances (e.g. pain)
Rigidity	Reduced eye blink	Mood disorders (e.g. depression)
Gait distrubance/Postural instability	Soft voice (Hypophonia)	Sleep Disturbances
	Dysphagia	Autonomic disturbances
	Freezing	Orthostatic hypotension
		GI disturbances
		GU disturbances
		Sexual dysfunction
		Cognitive impairment/Dementia

Table 372-2: Differential Diagnosis of Parkinsonism

Parkinsonism			
Parkinson's Disease	Atypical parkinsonisms	Secondary parkinsonism	Other Neurodegenerative Disorders
Genetic	Multiple System Atrophy	Drug induced	Wilson's Disease
Sporadic	Cerebellar type (MSA-c)	Tumor	Huntington's Disease
Dementia with Lewy Bodies	Parkinson type (MSA-p)	Infection	Neurodegeneration with brain iron accumulation
	Progressive supranuclear palsy	Vascular	SCA 3 (spinocerebellar ataxia)
	Corticobasal Ganglionic Degeneration	Normal pressure hydrocephalus	Fragile x associated ataxia-tremor-parkinsonism
	Frontotemporal Dementia	Trauma	Prion disease
		Liver failure	dystonia-parkinsonism (DYT3)
		Toxins	Alzheimer's disease with parkinsonism
		(e,g, carbon monoxide, manganese, MPTP cyanide, hexane, methanol, carbon disulfide	

Table 372-3

Features suggesting alternate diagnosis than PD

Symptoms/Signs	Alternative Diagnosis to Consider
History	
Early speech and gait impairment	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson's disease, Non-wilsonian hepatolenticular degeneration
Early hallucinations	Dementia with Lewy bodies
Diplopia	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Exam	
Dementia as first symptom	Dementia with Lewy bodies
Prominent orthostatic hypotentsion	MSA-p
Prominent cerebellar signs	MSA-c
Impairment of down gaze	PSP
High frequency (8–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Table 372-4: Genetic causes of PD

Name	Chromosome	Locus	Gene	Inheritance
Park 1	Chr 4	q21-23	a-synuclein	AD
Park 2	Chr 6	q25-27	Parkin	AR
Park 3	Chr 2	p13	Unknown	AD
Park 4	Chr 4	q21-23	a-synuclein	AD
Park 5	Chr 4	p14	UCHL-1	AD
Park 6	Chr 1	p35-36	PINK-1	AR
Park 7	Chr 1	p36	DJ-1	AR
Park 8	Chr 12	p11-q13	LRRK2	AR/Sp
Park 9	Chr 1	p36	ATP13A2	AR
Park 10	Chr 1	p32	Unknown	Sp
Park 11	Chr 2	q36-37	GIGYF2	AD
Park 12	Chr X	q21-25	Unknown	Sp
Park 13	Chr 2	p13	Omi/HtrA2	AD
Park 14	Chr 22	q13	PLA2G6	AR
Park 15	Chr 22	q12-13	FBX07	AR
Park 16	Chr 1	q32	Unknown	SP

AD: autosomal dominant, AR: autosomal recessive, SP: sporadic

Table 372- 5

Drugs commonly used for treatment of PD*

Agent	Available dosages	Typical dosing
Levodopa*		
Carbidopa/levodopa	10/100, 25/100, 25/250	200-1000 mg levodopa/day 2-4 times per da
Benserazied/levodopa	25/100, 50/200	
Carbiodpa/LevodopaCR	25/100, 50/200	
Benserazide/LevodopaMDS	25/200, 25/250	
Parcopa	10/100, 25/100, 25/250	
Carbidopa/levodopa/entacapone	12.5/50/200,18.75/75/200,25/100/200,31.25/125/200,37.5/150/200,50/200/2	
Dopamine agonists		
Pramipexole	0.125, 0.25mg, 0.5mg, 1.0mg, 1.5	0.25-1.0mg tid
Pramipexole ER	0.375, 0.75, 1.5. 3.0, 4.5	1-3 mg/day
Ropinirole	0.25, 0.5, 1.0, 3.0,	6-24mg per day
Ropinirole XL	2,4,6,8	6-24mg per day
Rotigotine patch	2,4,6 mg patches	4-10 mg per day
Apomorphine sc		2-8 mg
COMT inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100mg, 200mg	100-200mg tid
MAO-B inhibitors		
Selegiline	5mg	5 mg bid
Rasagiline	0.5mg, 1.0mg	1.0 mg QAM

*Treatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose. Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.

Table 372-6: Hyperkinetic Movement Disorders

Tremor	Rhythmic oscillation of a body part due to intermittent muscle contractions
Dystonia	Involuntary patterned sustained or repeated muscle contractions often associated with twisting movements and abnormal posture.
Athetosis	Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands
Chorea	Rapid, semi-purposeful, graceful, dance-like non-patterned involuntary movements involving distal or proximal muscle groups
Myoclonus	Sudden, brief (<100msec), jerk-like, arrhythmic muscle twitches
Tic	Brief, repeated, stereotyped muscle contractions that are often suppressable. Can be simple and involve a single muscle group or complex and affect a range of motor activities

Figure 372-1

Pathologic specimens from a patient with Parkinson's disease compared to a normal control demonstrating a) reduction of pigment in SNc in PD vs control, b) reduced numbers of cells in SNc in PD compared to control, and c) Lewy bodies (arrows) within melanized dopamine neurons in PD.

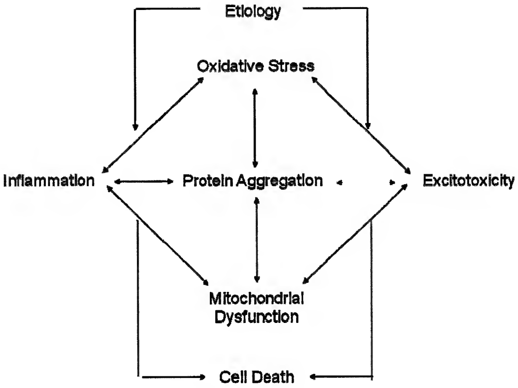
Figure 372-2: Basal Ganglia Nuclei

Schematic and Post mortem coronal sections illustrating the various components of the basal ganglia. SNc = Substania Nigra Pars Compacta, STN = Subthalamic Nucleus,

Figure 372-3: Fluorodopa-PET in a normal individual (left) and a PD patient (right).

Striatal FD-PET provides a measure of the integrity of the nigrostriatal system. Note reduced striatal uptake in PD compared to a control which tends to be more pronounced in the caudate than in the putamen (courtesy Dr. Jon Stoessl).

Figure 372 - 4



Schematic representation of how pathogenetic factors implicated in PD interact in a network manner ultimately leading to cell death. This figure illustrates how interference with any one of these factors may not necessarily stop the cell death cascade. (Adapted from Olanow, Movement Disorders, 2007).

Figure 372-5: Basal ganglia organization

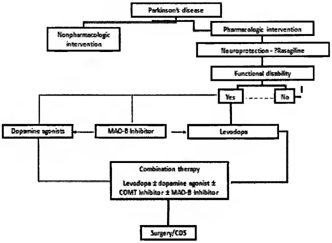
Classic model of the organization of the basal ganglia in the normal, PD, and levodopa-induced dyskinesia state. Inhibitory connections are shown as blue arrows and excitatory connections as red arrows. (TO THE EDITORS: THE ARROW FROM THE CORTEX TO THE PUTAMEN SHOULD BE RED – COULD YOU MAKE THIS CHANGE). The striatum is the major input region and receives its major input from the cortex. The GPi and SNr are the major output regions and they project to the thalamo-cortical and brain stem motor regions. The striatum and GPi/ SNr are connected by direct and indirect pathways. This model predicts that parkinsonism results from increased neuronal firing in the STN and GPi, and that lesions or DBS of these targets might provide benefit. This concept led to the rationale for surgical therapies for PD. The model also predicts that dyskinesia results from decreased firing of the output regions resulting in excessive cortical activation by the thalamus. This component of the model is not completely correct as lesions of the GPi ameliorate rather than increase dyskinesia in PD, suggesting that firing frequency is just one of the components that lead to the development of dyskinesia (derived from Olanow CW, Obeso JA, Nutt J. Basal ganglia, parkinson's disease and levodopa therapy. Supplement to Trends in Neuroscience 2000; Vol 23: Number 10).

GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; SNr, substantia nigra, pars reticulata; SNc, substantia nigra, pars compacta; STN, subthalamic nucleus; VL, ventrolateral thalamus; PPN, pedunculopontine nucleus.

Figure 372-7: Levodopa induced motor complications. Schematic illustration of the gradual shortening of the duration of a beneficial motor response to levodopa (wearing off) and the appearance of dyskinesias complicating "on" time.

Figure 372-6

Decision tree for the management of PD



Treatment Options for the Management of PD: Decision points include

a) Introduction of a neuroprotective therapy: No drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this potential based on laboratory and preliminary clinical studies (e.g. rasagiline 1mg/day, co-enzyme Q10 1200mg/day, the dopamine agonists ropinirole and pramipexole).

b) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because patients may have some disability even at an early stage and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy.

c) What therapy to initiate: Many experts favor starting with: an MAO-B inhibitor in mildly affected patients because of the potential for a disease-modifying effect; dopamine

agonists for younger patients with functionally significant disability to reduce the risk of motor complications; and levodopa for patients with more advanced disease, the elderly or those with cognitive impairment.

d) Management of motor complications: Motor complications are typical approached with combination therapy to try and reduce dyskinesia and enhance the on time. When medical therapies cannot provide satisfactory control, surgical therapies can be considered.

e) Non pharmaceutical approaches: Interventions such as exercise, education, and support should be considered throughout the course of the disease.

Figure 372-7

Gross brain specimens from a normal patient (right) and a patient with Huntington's disease (left). Note the marked ventricular enlargement and the prominent atrophy of the caudate nucleus (single arrow) and putamen (double arrows) in HD.

EXHIBIT H

Movement Disorders
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The Sydney Multicenter Study of Parkinson's Disease: The Inevitability of Dementia at 20 years

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Abstract: After 20 years follow-up of newly diagnosed patients with Parkinson's disease (PD), 100 of 136 (74%) have died. The mortality rate fell in the first 3 years of treatment, then rose compared to the general population, the standardized mortality ratio from 15 to 20 years reaching 3.1. Drug induced dyskinesia and end of dose failure were experienced by most patients, but the main current problems relate to the non-levodopa responsive features of the disease. Dementia is present in 83% of 20-year survivors. Dementia correlates with increasing age and probably reflects an interplay of multiple pathologies. Seventeen people with dementia had postmortems. Eight had diffuse Lewy bodies as the only cause of dementia, while others had mixed neuropathology. Only one person lives independently and 48% are in nursing homes. Excessive daytime sleepiness is noted in 70%, falls have occurred in 87%, freezing in 81%, fractures in 35%, symptomatic postural hypotension in 48%, urinary incontinence in 71%, moderate dysarthria in 81%, choking in 48%, and hallucinations in 74%. The challenge is to understand the cellular mechanisms underlying the diverse features of advanced PD that go far beyond a lack of dopamine. © 2008 Movement Disorder Society

Key words: Parkinson's disease; progression; dementia; mortality

Parkinson's disease (PD) is more than a nigrostriatal disorder. Although bradykinesia, tremor, and rigidity respond to dopaminergic therapy many other features do not. These include autonomic failure, hypersomnolance, imbalance, dysarthria, and dysphagia. These and most notably dementia and drug-related neuropsychiatric symptoms are what cause the most concern as the disease advances.[1] Although James Parkinson stated in *An Essay on the Shaking Palsy* that the intellect was "uninjured," he himself noted that, "at the very last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release."[2] This is still the picture that we see in late PD with dementia affecting most of those who do not die earlier of other causes.

How common dementia is in PD is a matter of debate. Studies from the prelevodopa era include those of Lewy, who in 1923 reported that 54 of 70 (77%) developed dementia and Monroe, who in 1951 noted that a third of people with PD aged over 61 developed a psychosis.[3] Nowadays, the prevalence of dementia in community-based studies is about 30%,[4] but ranges from about 10 to 80% of people with PD.[5,6] The older the patient and longer the duration of disease, the higher the prevalence of dementia.[7–9] Even in young onset, PD (21–40 years) dementia affects 19% after a median of 18 years.[10] Cognitive decline is noted in up to 36% of newly diagnosed cases of PD.[11,12] Dementia adds substantially to the burden of disease for the patient, caregiver, and the community.[13–15]

The Sydney Multicenter Study of PD is unique in having one group of clinicians follow a single cohort of newly diagnosed people with PD over 20 years. The aims of this report are to provide information on the rate

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of appearance of dementia and the other non-levodopa responsive features of PD, and on the mortality rate.

PATIENTS AND METHODS

The design and the progression of the study have previously been reported at 5, 10, and 15 years.[1,11,16,17] Sydney neurologists were asked to refer their newly diagnosed PD patients for a 5-year trial comparing low-dose bromocriptine with low-dose levodopa–carbidopa. Between 1984 and 1987,149 denovo PD patients who were Hoehn–Yahr stage 1 to 3 and aged 39 to 79 years were recruited from 29 neurologists. Diagnosis of PD was based on the presence of two of the following: bradykinesia, rigidity and resting tremor in the absence of features suggestive of atypical PD. Patients were not excluded if they had intercurrent disease as long as it was not in the terminal stages. All were living in the community. After the first 6 months of drug titration, the patients were also followed by their referring neurologists.

At their base line neuropsychological assessment, 26 were found to be demented, though in all cases the presentation to their referring neurologist had been with parkinsonism not dementia or hallucinations. These patients would now be labeled as having Dementia with Lewy bodies (DLB). However, all patients considered as having PD by the London Brain Bank criteria[18] were included in the study. Thirteen patients were excluded on the basis of having atypical PD (leaving 136). Six patients have been lost to follow-up (leaving 130).

Patients were examined in outpatient clinics for the first 10 years, but at 15 and 20 years were often examined in their home or nursing home if they were too frail to visit hospital. Telephone interviews with the patient and carer and reports of treating physicians were obtained for four people who had moved from Sydney. Neurological assessments have previously been reported.[16] Excessive daytime sleepiness was considered present if the patient had multiple sleeps during the daytime hours.

Detailed neuropsychological assessment was performed on 110 patients at study entry by the neuropsychologist (WR) and at 3, 5, 10, 15, and 20 years for people with English as their main language. The neuropsychological assessment battery was designed to sample a range of cognitive domains. Details of the tests and administration have been previously reported and neuropsychological findings will be the subject of a separate paper.[11] At the 15- and 20-year follow-up the minimental state examination (MMSE), Clinical Dementia Rating (CDR), and the Boston Naming Test were added to the battery.[19–22] Depression was assessed by the 30 item Geriatric Depression Scale (GDS).[23] Hallucinations were detected by routine questioning at each visit of the patient, and carer when present. Hallucinations were defined as a perception in the absence of an external stimulus and included presence, passage, complex visual, and auditory hallucinations. Illusions were also included as the altered perception of an external stimulus.

Cognitive function in patients who were not seen by the neuropsychologist was assessed by the neurologist (MH). The MMSE, similarities, letter fluency (words beginning with "f", "c", and "s" each in 1 min; normal >9 for each),[24] category fluency (animals normal >17) and clock faces were recorded at 15 and 20 years. Clock face drawing was scored from 0 to 4 with 1 point each for a closed circle, all 12 numbers, numbers in correct positions and hands correctly placed. Perseveration was tested for by asking patients to copy a three-loop spiral. A Clinical Dementia Rating was recorded after interview with family members regarding memory and other cognitive functioning and its impact on daily life. A neuropsychological diagnosis of dementia was made on the basis of impairment in memory and at least two other areas of cognitive functioning. A test score that decreased at least two standard deviations from the mean score obtained by the control group signified cognitive impairment. The control group consisted of 50 age, gender, and education matched community living people without PD, who were friends or relatives of the patients. If no neuropsychological assessment was made, a diagnosis of dementia was based on a Clinical Dementia Rating ≥1 with supporting evidence from carers of gradual cognitive decline sufficient to impair daily function. This was supported by abnormalities in MMSE, letter and category fluency, and clock face drawing.

On several occasions during the study, patients were asked to consider donating their brains for diagnostic and research purposes. Informed consent was obtained from the patient and family. The brain donation program at the Prince of Wales Medical Research Institute has both institutional and ethical approval and complies with the guidelines of the National Health and Medical Research Council of Australia. Brain only autopsy was performed and standard neuropathological methods and diagnostic criteria were used.[25]

Statistics

The time to event data are presented as Kaplan–Meier curves, where the time to event is censored at the end of

follow-up or death if the event has not occurred by that time. For the mortality analysis, the expected number of deaths is the number of deaths expected given the age and sex specific death rates seen in the general Australian population; these rates vary with calendar year, which has been taken into account for the calculations. The standardized mortality ratio (SMR) is the ratio of the observed and expected number of deaths and has been analyzed using Poisson regression. These analyses were performed in Stata (*Version 9*).[26]

RESULTS

Thirty patients (15 men and 15 women) have survived to be included in the 20-year follow-up that ranged from 19.8 to 22 years. Their average age is now 74 years (SD = 7.9), and was 54 years at presentation compared to 62 years for the initial total group.

Mortality

By 20 years, 100 of 136 (74%) had died and three have died since. In the first 3 years, five died compared with an expected 9.2 deaths (SMR = 0.5, 95% CI 0.2–1.1). Between 3 and 20 years, 95 died compared with an expected 38.7 deaths (SMR = 2.5, 95% CI = 2.0–3.0). The SMR was similar for the periods 3 to 5, 5 to 10, 10 to 15, and 15 to 20 years (chi-square test statistic for between period differences = 2.6 for 3 degrees of freedom, $P = 0.5$) but showed a trend to increase with duration of disease compared to the age matched Australian population after falling in the early years of treatment: SMR = 0.5 at 0 to 3 years, 1.8 at 3 to 5 years, 2.3 at 5 to 10 years, 2.7 at 10 to 15 years and 3.1 at 15 to 20 years. The SMR did not show variation with age and sex (chi-square test statistic for differences with sex or age = 1.0 for 2 degrees of freedom, $P = 0.6$).

The mean age at death was 76 years (SD = 7.5), 75 years for men and 78 years for women after a mean of 121 and 132 months from entry to the study, respectively. The difference between genders is not significant when compared with the longer survival of women in the general population. The median time from historical onset of disease to death was 12.4 years. Pneumonia was the most common cause of death, 26 of 103 (25%), generally occurring in Hoehn and Yahr stage 5. PD was considered to have been a significant contributor to the death of 55 of 103 (54%). A survival curve is shown in Figure 1.

L-Dopa-Induced Motor Complications

The mean levodopa intake is 729 mg/day (SD = 453) with a daily average of 4.7 intakes at 20 years.

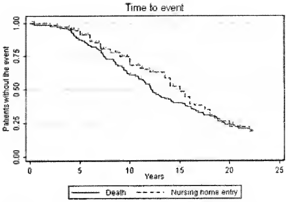

FIG. 1. Kaplan–Meier plot of time to death and of nursing home placement.

Eleven still take bromocriptine or an alternative agonist (mean dose equivalent to 18 mg/day (SD = 8) bromocriptine). No patients took anticholinergic medications at 20 years but 3 used selegiline, 7 entacapone, and 5 amantadine. All of those on at least 300 mg of levodopa per day had experienced end of dose failure and dyskinesia. At 20 years, dyskinesia was graded as mild to moderate (UPDRS 1–2) for both duration and severity in all, but 3 patients where it was graded as 3. Three others had pallidotomies for dyskinesia. Sudden "offs" were reported by 5 of 30 and an equal number lacked a good "on" due to inadequate levodopa dosage because of dementia. All others were on for more than half the day.

Hoehn and Yahr Stage and Level of Independence

At 20 years, the mean Hoehn and Yahr stage "on" was 4.2 and "off" was 4.6. Only 1 patient was stage 2 when "on," and he was the only patient living alone. Now aged 65, he was the last patient to cease work just prior to 15 years of disease. Two patients were stage 3 when "on," 15 stage 4, and 12 stage 5. Fourteen lived with family or had fulltime live in carers. Fifteen people (48%) lived in nursing homes. A survival curve for nursing home placement is shown in Figure 1. Patients lived there for a mean of 34 months (SD = 27) before death. The mean activities of daily living score (UPDRS items 5–17) "on" was 19 (SD = 8) and "off" was 27 (SD = 8). Excessive daytime sleepiness was recorded in 21 (70%).

Falls, Fractures, and Freezing

Falls were experienced by 27 (87%) of the 20 year survivors and 11 (35%) had sustained fractures, often

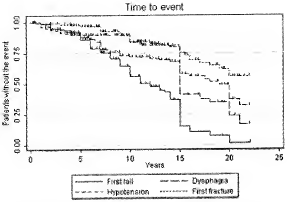

FIG. 2. Kaplan-Meier plot of time to falls, dysphagia, symptomatic postural hypotension, and first fracture.

multiple. This was in spite of active interventions with physiotherapy, walking aids, and home modification. Survival curves for these features are shown in Figure 2. Freezing occurred in 25 people (81%).

Bladder, Bowels, Blood Pressure, and Bulbar Problems

At 20 years autonomic problems were common with 15 (48%) noting symptomatic postural hypotension, although only 6 required fludrocortisone. Urinary incontinence occurred in 22 (71%), fecal incontinence in 5 (17%), and constipation requiring daily laxatives was present in 12 (40%). Dysarthria (>UPDRS1) was present in 25 (81%), 13 gade 3 and 2 gade 4. Choking was present in 15 (48%). Survival curves for dysphagia and postural hypotension are shown in Figure 2.

Hallucinations and Other Psychiatric Problems

In this group of 20-year survivors, visual hallucinations occurred in 23 (74%) necessitating reduced dopaminergic medication in all, introduction of atypical antipsychotics in 10 (7 quetiapine, mean dose 43 mg/day; 2 olanzapine 10/mg/day; 1 risperidone 1 mg/day) and cholinomimetics in 3 (2 donepezil 10/mg/day; 1 galantamine 16 mg/day). Of the original cohort, 78 were known to have suffered visual hallucinations prior to death, see Figure 3. One patient was physically violent in a psychotic episode. One patient had committed suicide. Two patients developed gambling problems after 10 years of treatment. One had hypersexuality. Other hedonistic behaviors were not noted. Depression was not formally assessed in all patients at 20 years due to cognitive decline, however, 15 (50%) were using antidepressants all at the recommended starting dose or less (8 on serotonin reuptake inhibiters and 7 on tricyclics). Seven of the 10 patients able to be assessed with the GDS showed evidence of depression (mean17, range 11–25).

Dementia

At 20 years, 25 of 30 (83%) surviving patients are demented and 2 have developed dementia after this. The increasing prevalence of dementia is shown in Figure 3. Table 1 shows the pattern of deficits in tests performed by the neurologist compared to the CDR. Results of the neuropsychological assessments will be the subject of a separate paper. However, the neuropsychological assessment confirmed dementia in 5 of 30 prior to 20 years and 11 others at 20 years. Eleven were not seen neuropsychologically in the last 5 or more years necessitating the use of the CDR and MMSE. Three of the 5 listed as CDR 0–0.5 were tested neuropsychologically, and did not meet neuropsychological criteria for dementia. Another 70 patients were demented before they died prior to 20 years, giving a total of 97 (75%) demented predeath. Of the patients who died never having demented, 14 did so early in the course of their PD from unrelated causes. Sixteen died more than 1 year after their last assessment so that their cognitive state just prior to death was unknown.

The mean age at time of diagnosis of dementia was 71.5 years for those 26 demented at presentation (DLB) and 71.6 years for those diagnosed later (PDD). There were 6 people aged 50 to 59 years at the time dementia was diagnosed, 27 aged 60 to 69 years, 56 aged 70 to 79 years, and 8 aged 80 to 89 years, see Figure 4. Excluding those demented at baseline, the mean follow-up until dementia intervened was 10.9

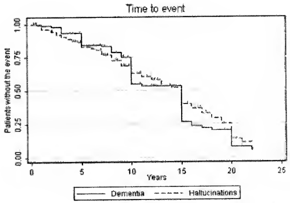

FIG. 3. Kaplan–Meier plot of time to hallucinations and dementia.

TABLE 1. *Comparison of CDR, MMSE, and brief cognitive testing for patients examined at 20 years*

CDR	No.	Age at 20 years	MMSE	Mean letter fluency $N > 9$	Animal category fluency, $N > 17$	Mean clockface normal = 4	Const. apraxia (%)	Perseveration (%)
0–0.5	5	64	29	8	19	4	0	20
1	15	75	25	6	11	3	80	60
2	5	76	14	1	4	1	100	100
3	5	79	2	0	1	0	100	100

years (SD = 5.5). Once dementia was diagnosed (excluding those diagnosed at baseline), the median survival was 54 months.

Neuropathology

Brain only postmortems were performed for 17 patients who died with dementia (mean age at death 79) and for 4 who died without dementia early in their course from unrelated health problems (mean age at death 70). All had brainstem Lewy body pathology consistent with the diagnosis of PD. Additional large vessel disease and hippocampal sclerosis were found in each of one case without dementia. Limbic and/or neocortical Lewy bodies were prominent features in 8/17 with dementia. In addition to limbic/neocortical Lewy bodies, 3/17 fulfilled NIA-Regan criteria for Alzheimer's disease (AD) and 2 of these had vascular disease including amyloid angiopathy. This latter was also present in 3/17 others as the most prominent additional neuropathology to PD. One had frontotemporal lobar degeneration with Pick bodies as well as PD.[25]

DISCUSSION

This is the longest prospective study of PD and is based on 136 newly diagnosed community living patients referred by 29 neurologists in Sydney from diverse social and educational backgrounds. The referring neurologists also continued to manage the patients after the initial drug study. The average age at presentation (62 years, range 37–79) was similar to other studies of this period.[18,27] We feel that these patients are representative of the general PD population.

When patients reach the later stages of their disease, physical frailty and cognitive decline mean they can no longer attend hospital clinics and private neurologists. Their extreme disability is therefore a hidden problem. In this group, only 14/30 (47%) still see their neurologist after 20 years. The later disease stages can often last 5 years and so, at their most vulnerable period, patients with PD are often lacking specialist care. Careful adjustment of medication can markedly improve quality of life even for the nursing home patient, for example, reducing cognitive side effects or dyskinesia. An outreach service from health professionals with knowledge of PD would be of value.

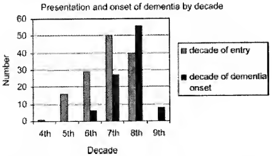

FIG. 4. Decade of presentation to the study and of dementia. Age over 80 was an exclusion criteria of the study.

Mortality

It is notable that, although not statistically significant, mortality briefly declines in the early years of treatment then continues to rise with the increasing duration of disease. This presumably reflects disease progression and the appearance of disease features that do not respond to our current medications such as falls, fractures, dysphagia (leading to pneumonia), autonomic failure, and dementia. All of these increase in prevalence after 10 years of disease and are not discussed here, as they formed the basis of the 15-year report.[1]

Dementia

Dementia occurred in almost every patient, even in those with a younger onset of disease, who did not succumb to intercurrent disease. The current article includes the whole available group using the neurologist's cognitive assessment to supplement the neuropsychological findings, as not all patients were assessed neuropsychologically. Direct comparison of the neurologist's and neuropsychologist's diagnosis of dementia revealed that neurologists are more likely to underestimate than overestimate the prevalence of dementia in their PD patients as neuropsychological

criteria were at times reached before the MMSE fell below 25 or the neurologist was aware of significant decline in social functioning. Neuropsychological assessment early is invaluable in detecting cognitive decline and guiding interventions but is not readily available in the community. Our findings suggest that unless dementia is actively sought and excluded, it should not be assumed to be absent. It is notable that while it is accepted that the MMSE is a poor tool for examining cognitive decline in PD with dementia (PDD), the CDR scale also tended to under-diagnose dementia (usually rating people 0.5, cognitive decline but not dementia) compared to the formal neuropsychological assessment. The latter is taken for the diagnosis of dementia where performed.

Clinical criteria for the diagnosis of PDD have recently been proposed that include the core features of idiopathic PD and a slowly progressive dementia syndrome that includes impairment in more than 1 cognitive domain that is a decline from premorbid levels. Cognitive deficits must be severe enough to impair daily functioning independent of deficits due to motor or autonomic failure.[28] Memory loss is not essential for diagnosis unlike DSM IV criteria or as defined in our neuropsychological diagnosis. Although memory loss is noted to occur commonly as the dementia progresses, it is not always an early feature.[29] As in our cases, it is clearly of value to have continuity of follow-up to detect the evolution of these changes and to be able to weight the various contributions of cognitive, autonomic, and motor deficits that impair the social, personal, and occupational functioning of people with PD. The history of a carer is also invaluable and delirium from drugs or systemic illness, and major depression need exclusion. Although neuroimaging may show changes of vascular disease in this older population, the typical insidious onset of PDD suggests that this is usually not the major cause. Extreme bradykinesia with poor motor skills and dysarthria can hamper cognitive assessment late in PD. It is, therefore, essential to perform serial brief regular assessments throughout the disease course to detect cognitive decline, and we encourage neurologists to add some of the simple tests used here to their assessments.

The prevalence of dementia in PD is poorly appreciated in the wider neurological community. It behoves neurologists to examine patients with PD most carefully for dementia as it has a number of consequences including: its association with drug and procedure induced hallucinations and psychoses; excessive daytime sleepiness and carer distress; loss of insight and poor judgment; the inability of patients to make sound financial decisions; impairment of driving skills; unreliability in following advice concerning medication; visuospatial problems that contribute to an increased risk of falls and fractures; unsuitability for deep brain stimulation, and it should suggest that elective surgery for intercurrent problems is best avoided. In association with increasing age, dementia and hallucinations predict nursing home placement.[1] Although dementia was predictive of death ($P = 0.001$) univariately, it is so strongly associated with increasing age as to render it insignificant when age is corrected for multivariately.[17] When correcting for severity of motor symptoms, Levy et al. found that incident dementia was associated with a doubling of mortality risk in a group of older PD patients.[30]

Dementia is unusual in younger patients at presentation. At baseline, 8% of patients aged 40 to 69 showed evidence of dementia by neuropsychological criteria. However, dementia was found in 39% of those aged 70 to 79 years at presentation.[11] Today, these people would be called DLB, although their presenting symptoms were motor, not dementia or hallucinations. These patients died early and so do not feature in the percentages of demented patients at 15 to 20 years. Others have also noted cognitive impairment in a proportion of patients with early PD.[12] The cognitive profile of PDD and DLB is very similar.[31] In a group with the early motor signs of PD, the London Brian Bank was unable to distinguish differences in the physical and cognitive signs and drug responsiveness of those with early dementia of DLB and later dementia of PDD.[32]

We had no patients with dementia in their 40s but 6 became demented in their 50s, including 1 at 53 after 8 years of disease but still alive at 20 years, and 1 at baseline at age 58 who at postmortem had AD and PD with limbic Lewy bodies. Dementia that is in excess of the general population has been noted in 19% of young onset patients (aged less than 40) after a median of 18 years on a telephone interview: 13% of those still aged under 60 and 43% of those aged over 60.[10] In contrast, 83% of our patients are demented after 20 years with an average age now of 74. The strong relationship to age, also noted by others,[8,33,34] rather than disease duration suggests that additional pathology to Lewy body parkinsonism may have a role in the appearance of dementia. A combination of pathologies is likely to be additive and thus cross the threshold for expression of dementia at an earlier stage than a single disease.

The neuropathology of dementia in PD is heterogeneous.[35–38] Staining for cortical Lewy bodies with α-synuclein suggests that limbic and cortical Lewy

bodies are the most important association of dementia in PD with or without additional Alzheimer's pathology.[37,39] However, the picture is complicated by the fact that neocortical Lewy body involvement does not always correlate with dementia in PD,[32] although high numbers of temporal and parahippocampal Lewy bodies may be better correlates of dementia in PD[40]; and the suggestion that Lewy body inclusions may represent a protective mechanism.[41] The fundamental cause of clinical dysfunction in PDD may lie within as yet undiscovered cellular mechanisms.[32]

In PDD, treatment is limited. Dopaminergic medication is frequently restricted by the appearance of visual hallucinations. Cholinergic deficits from the nucleus basalis of Meynert are believed to contribute to the fluctuations in levels of alertness in DLB[42] and cortical cholinergic loss is found to be more severe in PD than in AD.[43] This may explain the mild benefit noted in PDD from rivastigmine.[44,45]

CONCLUSION

In this 20-year study of 136 patients with PD, 30 survive. All have shown an improvement in motor function in response to dopaminergic therapy but clinical features, particularly dementia have now emerged for which this form of treatment is unhelpful. Until we have a better understanding of and can treat dysfunction in the nondopaminergic neuronal systems, we have less than we would wish to offer our patients with advanced PD. What we can offer is an early recognition of dementia and the other non-dopamine responsive problems to anticipate the measures that need to be taken to minimize their consequences for the patient and the carer. Ultimately, a cure for PD will depend on understanding the basic biochemistry of cellular dysfunction that affects so many aspects of the central and autonomic nervous systems.

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